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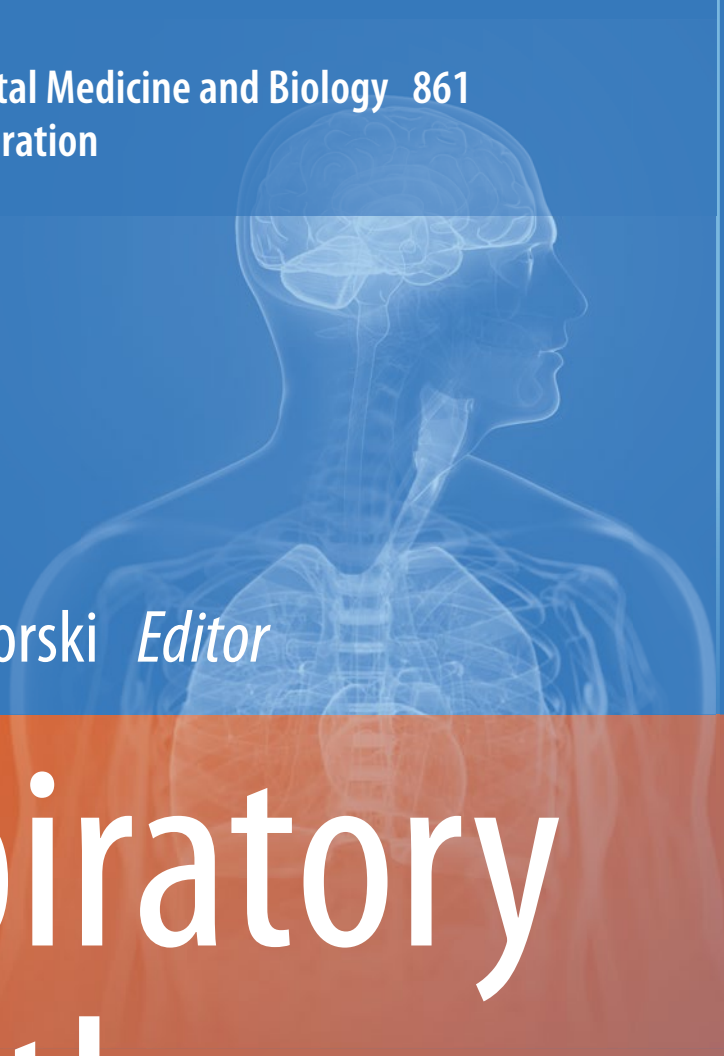
Neuroscience and Respiration



Mieczyslaw Pokorski *Editor*

Respiratory Health

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Respiratory Health

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Preface

The book series *Neuroscience and Respiration* presents contributions by expert researchers and clinicians in the field of pulmonary disorders. The chapters provide timely overviews of contentious issues or recent advances in the diagnosis, classification, and treatment of the entire range of pulmonary disorders, both acute and chronic. The texts are thought as a merger of basic and clinical research dealing with respiratory medicine, neural and chemical regulation of respiration, and the interactive relationship between respiration and other neurobiological systems such as cardiovascular function or the mind-to-body connection. The authors focus on the leading-edge therapeutic concepts, methodologies, and innovative treatments. Pharmacotherapy is always in the focus of respiratory research. The action and pharmacology of existing drugs and the development and evaluation of new agents are the heady area of research. Practical data-driven options to manage patients will be considered. New research is presented regarding older drugs, performed from a modern perspective or from a different pharmacotherapeutic angle. The introduction of new drugs and treatment approaches in both adults and children also is discussed.

Lung ventilation is ultimately driven by the brain. However, neuropsychological aspects of respiratory disorders are still mostly a matter of conjecture. After decades of misunderstanding and neglect, emotions have been rediscovered as a powerful modifier or even the probable cause of various somatic disorders. Today, the link between stress and respiratory health is undeniable. Scientists accept a powerful psychological connection that can directly affect our quality of life and health span. Psychological approaches, by decreasing stress, can play a major role in the development and therapy of respiratory diseases.

Neuromolecular aspects relating to gene polymorphism and epigenesis, involving both heritable changes in the nucleotide sequence and functionally relevant changes to the genome that do not involve a change in the nucleotide sequence, leading to respiratory disorders will also be tackled. Clinical advances stemming from molecular and biochemical research are but possible if the research findings are translated into diagnostic tools, therapeutic procedures, and education, effectively reaching physicians and patients. All these cannot be achieved without a multidisciplinary, collaborative, bench-to-bedside approach involving both researchers and clinicians.

The societal and economic burden of respiratory ailments has been on the rise worldwide, leading to disabilities and shortening of life span. COPD alone causes more than three million deaths globally each year. Concerted efforts are required to improve this situation, and part of those efforts are gaining insights into the underlying mechanisms of disease and staying abreast with the latest developments in diagnosis and treatment regimens. It is hoped that the books published in this series will assume a leading role in the field of respiratory medicine and research and will become a source of reference and inspiration for future research ideas.

I would like to express my deep gratitude to Mr. Martijn Roelandse and Ms. Tanja Koppejan from Springer's Life Sciences Department for their genuine interest in making this scientific endeavor come through and in the expert management of the production of this novel book series.

Opole, Poland Mieczyslaw Pokorski

Volume 14: Respiratory Health

The tracheobronchial tree is open to the environment surrounding the body. Respiration has thus the essential bearing on general morbidity, vulnerability to disease and immunity. Further, respiratory function shapes the neuropsychological responses to succumbing to disease, controls the mind-to-body interaction and sets the perception of quality of life. The chapters of this book deal with the preventable drivers of poor respiratory health, the role of health information technology, the improvement in health care delivery and the integration of respiratory health and behavioral health services. Innovative strategies to promote prevention, care coordination and care integration as well as to align disease acceptance and quality of life measures also are tackled. Maintaining respiratory health is of rising research interest as a way of preventing a disease or a non pharmacological therapeutic succor. The book will be of interest to clinicians, family practitioners and medical researchers.

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The Influence of Online Health Information on the Attitude and Behavior of People Aged 50+

M. M. Bujnowska-Fedak and D. Kurpas

Abstract

E-patients 'empowered' by Web information are much more likely to participate in health care decision processes and take responsibility for their own health. The purpose of the study was to determine the influence of Internet use and online health information on the attitude, behavior, and emotions of Polish citizens aged 50+, with special regard to their attitude towards health professionals and the health care system. A total of 323 citizens, aged 50 years and above, who used the Internet for health purposes, were selected from the Polish population by random sampling. The sample collection was carried out by Polish opinion poll agencies in 2005, 2007, and 2012. The Internet was used by 27.8 % of Polish citizens aged 50+ for health purposes in the years 2005–2012. 69.7 % of respondents were looking for health information that might help them to deal with a consultation, 53.9 % turned to the Internet to prepare for a medical appointment, and 63.5 % to assess the outcome of a medical consultation and obtain a 'second opinion'. The most likely effects of health related use of the Internet were: willingness to change diet or other life-style habits (48.0 % of respondents) and making suggestions or queries on diagnosis or treatment by the doctor (46.1 %). Feelings of reassurance or relief after obtaining information on health or illness were reported by a similar number of respondents as feelings of anxiety and fear (31.0 % and 31.3 % respectively). Online health information can affect the attitudes, emotions, and health behaviors of Polish citizens aged 50+ in different ways.

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Keywords
Attitude • Behavior • Eldercare • Emotions • E-patient • Health • Internet

1 Introduction

The world population is rapidly aging, which implies a significant increase in the demand for health care and social services. At the same time, the fast development of information and communication technologies (ICT) is being observed. The increasing relevance of the Internet is undeniable, and the use of Web-derived health information is rapidly growing (Pew Internet 2014; Seybert 2012; van Uden-Kran et al. 2009; Kummervold et al. 2008; Andreassen et al. 2007; Krane Harris Poll 2006). In many countries, the increase in the number of Internet health users is relatively larger than the increase due to the number of Internet users, and cannot be explained only by reference to improved Internet access (Pew Internet 2014; Kummervold et al. 2008; Krane Harris Poll 2006). Moreover, there has been a strong growth in e-health usage by the elderly (Pew Internet 2014; Ressi 2011; Kaiser Foundation 2004; Ferguson 2000) and their use of online health services is increasing faster than any other group (Wald et al. 2007; Campbell and Nolfi 2005; Ferguson 2000).

New e-health technologies empower citizens to exhibit behavior more challenging to the traditional passive model of doctor-patient relationship (Wald et al. 2007; Akerkar and Bichile 2004; Ferguson 2004). ICT tools provide opportunities for such patients, so-called 'e-patients', who see themselves as equal partners with their doctors in the healthcare process (Ressi 2011; Grant 2010; Hoch and Ferguson 2005). E-patients actively gather information about medical conditions using electronic communication tools to achieve full participation in health care decision-making processes (Ressi 2011; Grant 2010).

Health professionals and researchers no longer control the production and dissemination of medical information, and citizens have become co-producers of health information that is spread *via* different websites, emails, and virtual communities (Santana et al. 2011; van Uden-Kraan et al. 2009). Doctor-patient interaction often becomes influenced by what patients have learned via the Web. Physicians more often meet patients who expect their doctors to interpret their Internet-acquired information (Wald et al. 2007; Ziebland et al. 2004). Better informed and knowledgeable patients may be better prepared and more likely to ask doctors relevant and critical questions as a result of researching online health information (Santana et al. 2011; Ziebland et al. 2004). Therefore, the way in which online health information is presented and discussed during medical consultation can affect not only the course of the doctor-patient relationship, but also clinical outcomes (Wald et al. 2007; Bylund et al. 2007). A study performed among British primary care doctors has revealed that 75 % of physicians had patients who presented information retrieved from the Web at some point in time (Malone et al. 2004) and a Harris Poll showed that 52 % of adults who obtained health information online reported discussing this information with their doctor at least once (Krane Harris Poll 2006). Furthermore, 'the Cybercitizen Survey' conducted in the U.S. has shown that among 99 million 'empowered' American adults the Internet was used more frequently than a doctor (61.1 %), information found online at appointment was discussed with health professionals (54.7 %) and health decisions were changed based on information obtained online (45.8 %) (Ressi 2011). General practitioners report that the length of consultation has increased due to patient questions related to the information found on the Internet, and the expectations of patients who have consulted Internet medical

information are higher and sometimes unrealistic (Santana et al. 2011; McCaw et al. 2007; Murray et al. 2003).

Further research is needed to investigate the precise nature of the influence of medical information obtained from the Internet on patients' behavior and decision-making processes. Hence, the aim of the study was to determine the influence of Internet use and online health information on the attitude, behavior, and emotions of Polish citizens aged 50+, with special regard to their attitude towards health professionals and the health care system.

2 Methods

Respondents were provided with comprehensive information concerning the objectives and scope of the survey and gave their informed consent. The survey protocol was approved by the Bioethical Committee at Wroclaw Medical University, Poland (statutory activity 481/2010).

A total of 1,162 citizens aged 50 years and more were selected from the Polish population by random sampling. Data was obtained from a subsample of adults 50+ in three subsequent surveys of Internet use in Poland in 2005 (n = 366), 2007 (n = 368), and 2012 (n = 428), conducted among adults of all age categories (n = 3,027). The sample collection was carried out by the Polish opinion poll agencies (CBOS, TNS), using computer-assisted telephone interview (CATI) in November 2005, April 2007, and October–November 2012 subsequently. Random digital dialing in strata was used to ensure a randomized representative sample of the population. Quotas were constructed, based on census data for age, gender, and place of residence (size of the place of residence and region of the country) to make sure the data was representative in this regard. Both landline telephones and mobile phones were included in the survey. The poll agencies conducting the interview were instructed to follow standard procedures related to contact with a replacement if a person originally selected for interview was unavailable (i.e. because of incorrect phone number, not answering the phone, not at home, or unwilling to participate). No variables had more than 5 % missing data. Finally, among a sample of citizens 50+, a subgroup of 323 persons was chosen from respondents who answered positively to the question concerning use of Internet for health related purposes.

The questionnaire used in the study (the same in all three surveys) was designed for CATI. The subjects were asked to respond to questions investigating different aspects of use of the Internet for health purposes and consequences of its use. The frequency of some aspects of Internet use to better handle medical consultations was assessed by Set A of questions: Do you use the Internet to: (1) find health information that can help you decide whether to consult a health professional? (2) find health information prior to an appointment? (3) find information after an appointment with health professionals (e.g. for second opinion)? The response categories were "Always", "Often", "Sometimes", "Rarely", and "Never". For transparency of analysis, the initial five options were grouped into three categories: "Always or often", "Sometimes or rarely", and "Never". Different emotions triggered by using the Internet and researching online health information were measured by Set B of questions: (1) Do you worry about confidentiality related to use of the Internet? (2) Has the information on health or illness which you have obtained from the Internet led to feelings of anxiety? (3) Has the information on health or illness which you have obtained from the Internet led to feelings of reassurance or relief? The response categories were "Yes", "No", and "Do not know". For clarity of analysis, the responses "No" and "Do not know" were grouped into one category: "No/Undecided". The influence of online health information on citizens' attitudes and behaviors towards health professionals and health systems was assessed by Set C of questions: Has the information on health or illness which you have obtained from the Internet led to any of the following: (1) Willingness to change diet or other life style habits? (2) Suggestions or queries on diagnosis or treatment to your family doctor, specialist or other health professional? (3) Changing the use

of medicine without consulting your family doctor, specialist or other health professional? (4) Making, cancelling or changing an appointment with your family doctor, specialist or other health professional? The response categories were "Yes", "No" and "Do not know". The responses "No" and "Do not know" were grouped into one category: "No/Undecided". The questionnaire also contained items related to socio-demographic characteristics and health conditions (e.g. the age, gender, education, place of residence, Internet and mobile phone use, and chronic diseases of the respondent).

2.1 Statistical Analysis

Variables were compared in terms of their average scores to identify significant predictors. The type of distribution for all variables was determined. Two quantitative variables (age and numbers of doctor's visits during the previous 12 months) had no normal distribution, which was verified with the Shapiro-Wilk test of normality. Arithmetic mean, standard deviations, median, as well as the range of variability (extremes) were calculated for measurable (quantitative) variables, whereas for qualitative variables, a frequency (percentage) with a 95 % confidence interval was determined. A nonparametric Wilcoxon rank-sum test was conducted to compare the distribution of quantitative variables between groups studied (equivalent to the Mann-Whitney U test). For qualitative variables, Fisher's exact test for contingency tables, or the chi-squared test (when the computational complexity did not allow for the implementation of Fisher's exact test) were used to determine statistically significant dependencies. All tests were two-sided, and the significance level was set at 0.05. A statistical analysis was carried out with R version 3.0.2 (for Mac OS X 10.9.4) software.

Analyses were made within the total sample, in the subsamples of younger and older respondents, and subsamples of three subsequent surveys from 2005, 2007, and 2012. Studies of the total sample enabled the results for the population to be generalized, whereas study of the subsamples led to a better understanding of changes over time and factors affecting the attitudes and behaviors of the respondents.

3 Results

3.1 Characteristics of Respondents

Among a total of 1,162 citizens aged 50 years and over, 27.8 % of Polish citizens 50+ (n = 323) used the Internet for health related purposes, and were included into the study. The study group consisted of 164 males (50.8 %) and 159 females (49.2 %), and the median age was 56 (min-max: 50–83). Two age categories were taken into consideration: 50–59 years of age (n = 217) and 60 years of age and over (n = 106). Three subgroups corresponding to each of the surveys have also been highlighted: Internet users for health purposes (IUHP) 2005 (n = 56), IUHP 2007 (n = 96), and IUHP 2012 (n = 171). With respect to location, 34.8 % of total respondents (n = 112) lived in cities (over 100,000 residents), 34.9 % (n = 113) in towns, and 30.4 % in rural areas (n = 98). As far as employment status is concerned, 43.8 % (n = 141) of older citizens still had paid work, whereas 5.9 % (n = 19) were permanently sick or disabled. The median number of doctor's visits during the previous 12 months was 4 - (min-max: 0–99); and more than 90 % of citizens 50+ assessed their health as at least 'fair'. Further information on the study population is provided in Table 1.

3.2 Internet Use to Better Handle the Medical Consultation

70.3 % of citizens aged 50 and over were looking for health information that might help them take a decision as to whether to consult a health professional; 54.5 % turned to the Internet to find medical information prior to an appointment, and 63.8 % were looking for health information to assess the outcome of the medical consultation and get a 'second opinion'. The younger group of

Table 1 Selected demographic characteristics, health condition, Internet, and mobile phone use[a]

Characteristics	All respondents 50+ *n = 323* % (CI)	IUHP 50–59 *n = 217* % (CI)	IUHP 60+ *n = 106* % (CI)	IUHP 2005 *n = 56* % (CI)	IUHP 2007 *n = 96* % (CI)	IUHP 2012 *n = 171* % (CI)
Gender						
Men	50.8 (45.2–56.3)	46.5 (39.8–53.4)	59.4 (49.4–68.7)	62.5 (48.5–74.8)	56.2 (45.8–66.2)	43.9 (36.4–51.6)
Women	49.2 (43.7–54.8)	53.5 (46.6–60.2)	40.6 (31.3–50.6)	37.5 (25.2–51.5)	43.8 (33.8–54.2)	56.1 (48.4–63.6)
Age (years)						
Means ± SD	58.0 ± 7.1	54.0 ± 2.9	66.3 ± 5.7	57.2 ± 6.3	57.9 ± 7.6	58.4 ± 7.1
Median (min-max)	56 (50–83)	54 (50–59)	65 (60–83)	55 (50–77)	57 (50–79)	57 (50–83)
Education[a]:						
A level	26.9 (22.2–32.2)	27.6 (21.9–34.2)	25.5 (17.7–35.0)	17.9 (9.3–30.9)	22.9 (15.2–32.8)	32.2 (25.4–39.8)
B level	41.8 (36.4–47.4)	43.3 (36.7–50.2)	38.7 (29.5–48.7)	35.7 (23.7–49.7)	49.0 (38.7–59.3)	39.7 (32.5–47.5)
C level	31.3 (26.3–36.7)	29.1 (23.2–35.6)	35.8 (26.9–45.8)	46.4 (33.2–60.1)	28.1 (19.7–38.4)	28.1 (21.6–35.5)
Employment status						
Paid work (including self-employment)	43.8 (38.3–49.4)	57.9 (51.0–64.5)	15.1 (9.1–23.7)	51.8 (38.2–65.2)	46.9 (36.7–57.3)	39.4 (32.1–47.2)
Retired/housework/care for children or other persons/unemployed and others	50.3 (44.7–55.9)	35.2 (28.9–42.0)	81.1 (72.1–87.8)	41.1 (28.4–55.0)	45.8 (35.7–56.3)	55.9 (48.1–63.4)
Permanently sick or disabled	5.9 (3.7–9.2)	6.9 (4.1–11.4)	3.8 (1.2–9.9)	7.1 (2.3–18.1)	7.3 (3.2–14.9)	4.7 (2.2–9.4)
Place of residence						
Big cities (above 100,000 residents)	34.8 (29.6–40.3)	33.2 (27.0–39.9)	38.1 (28.9–48.1)	50.0 (37.3–62.7)	35.4 (26.1–45.9)	29.4 (22.8–37.0)
Minor cities	34.8 (29.6–40.3)	33.6 (27.5–40.4)	37.1 (28.1–47.2)	30.4 (19.2–44.3)	38.5 (29.0–49.1)	34.1 (27.1–41.8)
Villages/rural area	30.4 (25.5–35.8)	33.2 (27.0–39.9)	24.8 (17.1–34.3)	19.6 (10.7–32.8)	26.1 (17.9–36.2)	36.5 (29.3–44.2)
Health status (subjective assessment)						
Very good/ good	44.3 (38.8–49.9)	46.5 (39.8–53.4)	39.6 (30.4–49.6)	46.4 (33.2–60.1)	44.8 (34.8–55.3)	43.3 (35.8–51.1)
Fair	47.0 (41.5–52.7)	46.1 (39.4–53.0)	49.1 (39.3–58.9)	42.9 (30.0–56.7)	44.8 (34.8–55.3)	49.7 (42.0–57.4)
Poor /very poor	8.7 (5.94–1.4)	7.4 (4.4–11.9)	11.3 (6.2–19.3)	10.7 (4.4–22.6)	10.4 (5.4–18.7)	7.0 (3.8–12.2)
Frequency of visits to doctor (during last 12 months)						
Means ± SD	6.8 ± 9.8	6.6 ± 11.1	7.3 ± 6.5	6.8 ± 7.0	6.0 ± 7.1	7.3 ± 11.7
Median (min-max)	4 (0–99)	4 (0–99)	6 (0–45)	5 (0–30)	3 (0–30)	5 (0–99)

(continued)

Table 1 (continued)

Characteristics	All respondents 50+ *n = 323* % (CI)	IUHP 50–59 *n = 217* % (CI)	IUHP 60+ *n = 106* % (CI)	IUHP 2005 *n = 56* % (CI)	IUHP 2007 *n = 96* % (CI)	IUHP 2012 *n = 171* % (CI)
Chronic diseases/disability						
Yes, I personally	13.7 (10.2–18.0)	13.0 (8.9–18.4)	15.1 (9.1–23.7)	12.5 (5.6–24.7)	10.5 (5.4–18.9)	15.8 (10.8–22.3)
Yes, a person close to me	28.9 (24.1–34.2)	31.5 (25.4–38.2)	23.6 (16.1–33.0)	26.8 (16.2–40.5)	27.4 (19.0–37.6)	30.4 (23.7–38.0)
No	57.4 (51.8–62.9)	55.5 (48.7–62.3)	61.3 (51.3–70.5)	60.7 (46.8–73.2)	62.1 (51.5–71.7)	53.8 (46.0–61.4)
Frequency of Internet use for health purposes						
Every day	2.5 (1.2–5.0)	2.3 (0.9–5.6)	2.8 (0.7–8.7)	3.6 (0.6–13.4)	2.1 (0.4–8.0)	2.3 (0.8–6.3)
Every week	21.4 (17.1–26.3)	20.3 (15.3–26.4)	23.6 (16.1–33.0)	12.5 (5.6–24.7)	22.9 (15.2–32.8)	23.4 (17.4–30.6)
Every month	46.1 (40.6–51.7)	46.1 (39.4–53.0)	46.2 (36.6–56.1)	39.3 (26.8–53.3)	50.0 (40.2–59.8)	46.2 (38.6–54.0)
Every 6 months	19.2 (15.1–24.0)	18.9 (14.0–24.9)	19.8 (13.0–28.9)	12.5 (5.6–24.7)	20.8 (13.5–30.6)	20.5 (14.9–27.5)
Ever year	7.4 (4.9–11.0)	8.3 (5.1–13.0)	5.7 (2.3–12.4)	21.4 (12.0–34.8)	1.1 (0.1–6.5)	6.4 (3.4–11.5)
Less than once a year	3.4 (1.8–6.2)	4.1 (2.0–8.0)	1.9 (0.3–7.3)	10.7 (4.4–22.6)	3.1 (0.8–9.5)	1.2 (0.2–4.6)
Mobile phone use						
Yes	93.6 (88.5–96.6)	96.3 (90.3–98.8)	88.7 (77.5–95.0)			93.6 (88.5–96.6)
No	6.4 (3.4–11.5)	3.7 (1.2–9.7)	11.3 (5.0–22.5)	No data	No data	6.4 (3.4–11.5)

IUHP Internet users for health purposes

[a]The item related to the education of respondents included 11 options, from basic to university level, specific to the Polish education system. The 11 levels were collapsed into 3 categories according to the International Standard Classification of Education (ISCED): (A) education level lower than upper secondary; (B) education level including upper secondary to post-secondary non-tertiary; and (C) education level covering all levels according to ISCED higher than post-secondary non-tertiary

respondents (50–59) had a rather more proactive stance, and used the Internet for these purposes slightly more often when compared with older respondents (60+). However, this trend has statistical significance only in the case of searching for online health information prior to an appointment ($p = 0.017$). Analyzing subsequent surveys, citizens 50+ in 2012 used the Internet significantly more often than in 2005 and 2007: to find health information that could help them make a decision about consulting a health professional ($p = 0.030$), to be prepared for a medical consultation ($p = 0.035$) and to assess the outcome of the consultation with the doctor ($p = 0.008$) (Table 2).

3.3 The Influence of Online Health Information on the Attitudes and Behavior of Citizens 50+

Willingness to change diet or other life-style habits (48.0 % of positive answers), or making suggestions or queries on diagnosis or treatment to the doctor (46.1 %), were the most likely effects of health-related use of the Internet. Feelings of reassurance or relief after obtaining information on health or illness were reported by a similar number of respondents as feelings of anxiety and fear (31.0 % and 31.3 %, respectively). On the other hand, online health information caused 20.4 % of citizens aged 50 and over to make, change or cancel an appointment with a doctor, and 7.7 % of respondents took a critical decision to change their use of medicines without consulting their family doctor, specialist or any other health professionals. Concerns about confidentiality of transmitted data were expressed by 7.4 % of older citizens (Table 3).

Comparative analysis showed that the older group of respondents (60+) had significantly more concerns about the lack of confidentiality of contact *via* the Internet (4.9 % in IUHP 50–59 *vs.* 12.5 % in IUHP 60+, $p = 0.030$). At the same time, they felt anxiety caused by information obtained from the Internet significantly less often than the younger group of citizens (35.0 % in IUHP 50–59 *vs.* 23.6 % in IUHP 60+, $p = 0.041$). In subsequent surveys, the need for making suggestions or queries on diagnosis and treatment to a doctor, as a result of researching online information, had diminished, and citizens aged 50+ in 2012 discussed information obtained from the Internet with their doctors significantly less frequently than in previous years (57.2 % of respondents in 2005, 52.1 % in 2007, and 39.2 % in 2012, respectively, $p = 0.024$). Similarly, in 2012, older citizens had significantly more frequent feelings of anxiety caused by using the Internet than in 2005 and 2007 (30.4 % of respondents in 2005, 21.9 % in 2007, and 36.8 % in 2012, respectively, $p = 0.039$) (Table 3).

3.4 Factors Affecting the Attitudes and Behavior of Citizens 50+ Using the Internet for Health Purposes

Multivariate analysis of different factors influencing the attitudes and behavior of citizens aged 50 and over using the Internet for health related purposes was conducted, see Table 4, part 1 and 2. As regards sex, women reported significantly more feelings of anxiety ($p = 0.016$); as regards education, a low level of education was more frequently related to feelings of reassurance or relief ($p = 0.028$), and higher education with more frequent suggestions or queries on diagnosis or treatment to the doctor ($p = 0.05$). Citizens aged 50 years and over, living in rural areas, and suffering from chronic diseases or disability, had feelings of anxiety caused by Internet use significantly more often. The least common anxiety was found in people from smaller towns and with no chronic diseases/disability ($p = 0.044$ and $p = 0.024$, respectively). Furthermore, a higher frequency of visits to the doctors was related to more frequent changes of use of medicines without consulting a physician or other health professionals ($p = 0.043$). As would be expected, mobile phone use was significantly associated with reduced fear concerning confidentiality of contact *via* the Internet ($p = 0.009$). The relationship between older age and worries about confidentiality, together

Table 2 Frequency of some purposes related to medical consultation for which Internet can be used to provide information on health and/or illness

Purposes related to medical consultation	All respondents 50+ mean% (CI) *n =323*	IUHP 50–59 mean% (CI) *n = 217*	IUHP 60+ mean% (CI) *n = 106*	P-value	IUHP 2005 mean% (CI) *n = 56*	IUHP 2007 mean% (CI) *n = 96*	IUHP 2012 mean% (CI) *n = 171*	P-value
Finding health information to decide whether to consult a health professional								
Always/often	12.1 (8.8–16.3)	12.9 (8.9–18.3)	10.4 (5.5–18.2)		12.5 (5.6–24.7)	9.4 (4.6–17.5)	13.5 (8.9–19.7)	
Sometimes/rarely	58.2 (52.6–63.6)	59.0 (52.1–65.5)	56.6 (46.6–66.1)		53.6 (39.9–66.8)	50.0 (40.2–59.8)	64.3 (56.6–71.4)	
Never	29.7 (24.9–35.1)	28.1 (22.3–34.7)	33.0 (24.4–42.9)	0.613	33.9 (22.2–47.9)	40.6 (30.9–51.1)	22.2 (16.4–29.3)	0.030
Finding health information prior to an appointment (to be prepared for a medical consultation)								
Always/often	11.1 (8.0–15.2)	11.5 (7.7–16.7)	10.4 (5.5–18.2)		8.9 (3.3–20.4)	5.2 (1.9–12.3)	15.2 (10.3–21.7)	
Sometimes/rarely	43.3 (37.9–49.0)	48.4 (41.6–55.2)	33.0 (24.4–42.9)		39.3 (26.8–53.2)	40.6 (30.9–51.1)	46.2 (38.6–54.0)	
Never	45.5 (40.0–51.1)	40.1 (33.6–47.0)	56.6 (46.6–66.1)	0.017	51.8 (38.2–65.2)	54.2 (43.7–64.3)	38.6 (31.4–46.4)	0.035
Finding health information to assess the outcome of the medical consultation and get ‘second opinion’								
Always/often	13.6 (10.2–18.0)	14.3 (10.1–19.8)	12.3 (7.0–20.4)		14.3 (6.8–26.8)	6.2 (2.6–13.6)	17.5 (12.3–24.3)	
Sometimes/rarely	50.2 (44.6–55.7)	51.6 (44.8–58.4)	47.2 (37.5–57.1)		48.2 (34.8–61.8)	44.8 (34.7–55.3)	53.8 (46.0–61.4)	
Never	36.2 (31.0–41.8)	34.1 (27.9–40.9)	40.6 (31.3–50.6)	0.538	37.5 (25.2–51.5)	49.0 (38.7–59.3)	28.7 (22.1–36.1)	0.008

IUHP Internet users for health purposes

Table 3 Influence of Internet use and online health information on attitudes, behaviors, and emotions of Polish citizens 50+

Attitudes and behaviors	ALL RESPONDENTS 50+ mean% (CI) *n = 323*	IUHP 50–59 mean% (CI) *n = 217*	IUHP 60+ mean% (CI) *n = 106*	P-value	IUHP 2005 mean% (CI) *n = 56*	IUHP 2007 mean% (CI) *n = 96*	IUHP 2012 mean% (CI) *n = 171*	P-value
Worries about confidentiality								
Yes	7.4 (4.8–11.1)	4.9 (2.5–9.1)	12.5 (6.9–21.2)	0.030	7.4 (2.4–18.7)	4.5 (1.5–11.9)	8.9 (5.1–14.8)	0.484
No/Undecided	92.6 (88.9–95.2)	95.1 (90.9–97.5)	87.5 (78.8–93.1)		92.6 (81.3–97.6)	95.5 (88.1–98.5)	91.1 (85.2–94.9)	
Feelings of anxiety								
Yes	31.3 (26.3–36.7)	35.0 (28.8–41.8)	23.6 (16.1–33.0)	0.041	30.4 (19.2–44.3)	21.9 (14.3–31.7)	36.8 (29.7–44.6)	0.039
No/Undecided	68.7 (63.3–73.7)	65.0 (58.2–71.2)	76.4 (67.0–83.9)		69.6 (55.7–80.8)	78.1 (68.3–85.7)	63.2 (55.4–70.3)	
Feelings of reassurance or relief								
Yes	31.0 (26.0–36.4)	30.9 (24.9–37.5)	31.1 (22.7–41.0)	1	41.1 (28.4–55.0)	31.2 (22.4–41.6)	27.5 (21.1–34.9)	0.166
No/Undecided	69.0 (63.6–74.0)	69.1 (62.5–75.1)	68.9 (59.0–77.3)		58.9 (45.0–71.6)	68.8 (58.4–77.6)	72.5 (65.1–78.9)	
Willingness to change diet or other life style habits								
Yes	48.0 (42.4–53.6)	49.3 (42.5–56.1)	45.3 (35.7–55.2)	0.554	51.8 (38.2–65.2)	54.2 (43.7–64.3)	43.3 (35.8–51.1)	0.185
No/Undecided	52.0 (46.4–57.6)	50.7 (43.9–57.5)	54.7 (44.8–64.3)		48.2 (34.8–61.8)	45.8 (35.7–56.3)	56.7 (48.9–64.2)	
Suggestions or queries on diagnosis or treatment to the family doctor, specialists or other health professionals								
Yes	46.1 (40.6–51.7)	47.5 (40.7–54.3)	43.4 (33.9–53.4)	0.553	57.1 (43.3–70.0)	52.1 (41.7–62.3)	39.2 (31.9–47.0)	0.024
No/Undecided	53.9 (48.3–59.4)	52.5 (45.7–59.3)	56.6 (46.6–66.1)		42.9 (30.0–56.7)	47.9 (37.7–58.3)	60.8 (53.0–68.1)	
Changing of use of medicine without consulting the doctor or other health professionals								
Yes	7.7 (5.2–11.4)	6.9 (4.1–11.4)	9.4 (4.9–17.1)	0.506	7.1 (2.3–18.1)	8.3 (3.9–16.2)	7.6 (4.3–12.9)	0.960
No/Undecided	92.3 (88.6–94.8)	93.1 (88.6–95.9)	90.6 (82.9–95.1)		92.9 (81.9–97.7)	91.7 (83.8–96.1)	92.4 (87.1–95.7)	
Making, cancelling or changing an appointment with the doctor or other health professionals								
Yes	20.4 (16.3–25.3)	20.3 (15.3–26.4)	20.8 (13.7–29.9)	1	23.2 (13.4–36.7)	26.0 (17.9–36.2)	16.4 (11.3–23.0)	0.144
No/Undecided	79.6 (74.7–83.7)	79.7 (73.6–84.7)	79.2 (70.1–86.3)		76.8 (63.3–86.6)	74.0 (63.8–82.1)	83.6 (77.0–88.7)	

IUHP Internet users for health purposes

Table 4 Factors affecting the attitudes, behaviors, and emotions of citizens 50+ using the Internet for health related purposes; Part 1

Characteristics	Worries about confidentiality; mean % (CI)	No worries about confidentiality; mean % (CI)	P-value	Feelings of anxiety; mean % (CI)	No feelings of anxiety; mean % (CI)	P-value	Feelings of reassurance or relief; mean % (CI)	No feelings of reassurance or relief; mean % (CI)	P-value	Willingness to change diet or other life style habits; mean % (CI)	Lack of willingness to change life style habits; mean % (CI)	P-value
Gender												
Men	59.1 (36.6–78.5)	48.4 (42.4–54.4)		40.6 (31.1–50.8)	55.4 (48.6–62.0)		47.0 (37.0–57.2)	52.5 (45.7–59.1)		47.7 (39.7–55.9)	53.6 (45.7–61.2)	
Women	40.9 (21.4–63.3)	51.6 (45.6–57.6)	0.380	59.4 (49.2–68.9)	44.6 (38.0–51.4)	0.016	53.0 (42.8–63.0)	47.5 (40.9–54.3)	0.400	52.3 (44.1–60.3)	46.4 (38.8–54.3)	0.317
Age (years, means ± SD)	59.2 ± 6.1	57.8 ± 6.9	0.155	57.0 ± 6.1	58.5 ± 7.5	0.182	58.2 ± 6.3	58.0 ± 7.4	0.307	57.9 ± 6.5	58.2 ± 7.6	0.835
Education[a]:												
A level	18.2 (6.0–41.0)	27.1 (22.0–32.8)		29.7 (21.2–39.7)	25.7 (20.2–32.0)		37.0 (27.7–47.3)	22.4 (17.2–28.6)		23.2 (17.0–30.8)	30.4 (23.6–38.0)	
B level	63.6 (40.8–82.0)	41.2 (35.4–47.2)		36.6 (27.4–46.9)	44.1 (37.5–50.9)		36.0 (26.8–46.3)	44.4 (37.8–51.2)		42.6 (34.8–50.8)	41.1 (33.6–48.9)	
C level	18.2 (6.0–41.0)	31.8 (26.4–37.7)	0.159	33.7 (24.8–43.8)	30.2 (24.3–36.7)	0.448	27.0 (18.8–37.0)	33.2 (27.1–39.8)	0.028	34.2 (26.9–42.3)	28.6 (22.0–36.1)	0.313
Employment status												
Paid work	50.0 (30.7–69.3)	43.5 (37.6–49.6)		43.0 (33.3–53.3)	44.1 (37.5–50.9)		40.0 (30.5–50.3)	45.5 (38.9–52.3)		42.6 (34.8–50.8)	44.9 (7.3–52.8)	
Retired/housework/ care for children or other persons/ unemployed, and others	50.0 (30.7–69.3)	50.0 (44.1–55.9)		47.0 (37.0–57.2)	51.8 (45.0–58.5)		50.0 (40.4–59.6)	50.5 (43.7–57.2)		50.3 (42.2–58.4)	50.3 (42.5–58.1)	
Permanently sick or disabled	0.0 (0.0–8.5)	6.5 (4.0–10.3)	0.594	10.0 (5.2–18.0)	4.1 (2.0–7.8)	0.118	10.0 (5.2–18.0)	4.1 (2.0–7.8)	0.109	7.1 (3.8–12.7)	4.8 (2.2–9.5)	0.687
Place of residence												
Big cities (above 100,000 residents)	19.0 (6.3–42.6)	35.4 (29.8–41.4)		36.6 (27.4–46.9)	33.9 (27.8–40.6)		37.0 (27.7–47.3)	33.8 (27.7–40.5)		38.7 (31.1–46.9)	31.1 (24.3–38.8)	
Minor cities	47.6 (26.4–69.7)	33.6 (28.1–39.5)		25.7 (17.8–35.6)	38.9 (32.5–45.7)		36.0 (26.8–46.3)	34.2 (28.1–40.9)		31.6 (24.5–39.6)	37.7 (30.4–45.6)	
Villages/rural area	33.3 (15.5–56.9)	31.0 (25.7–36.9)	0.262	37.6 (28.3–47.9)	27.1 (21.5–33.6)	0.044	27.0 (18.8–37.0)	32.0 (26.0–38.6)	0.674	29.7 (22.8–37.6)	31.1 (24.3–38.8)	0.327

Type of residence												
Alone	0.0 (0.0–26.8)	11.9 (7.3–18.6)		11.1 (5.0–22.2)	11.1 (6.1–19.0)		10.6 (4.0–23.9)	11.3 (6.5–18.5)		10.8 (5.1–20.7)	11.3 (6.1–19.8)	
With family	100 (73.2–100)	88.1 (81.4–92.7)	0.367	88.9 (77.8–95.0)	88.9 (81.0–93.9)	1	89.4 (76.1–96.0)	88.7 (81.5–93.5)	1	89.2 (79.3–94.9)	88.7 (80.2–93.9)	1
Health status (subjective assessment)												
Very good/ good	40.9 (21.5–63.3)	44.0. (38.1–50.1)		34.7 (25.6–44.8)	48.6 (41.9–55.4)		40.0 (30.5–50.3)	46.2 (39.5–53)		43.9 (36.0–52.1)	44.6 (37.0–52.5)	
Fair	45.5 (25.1–67.3)	47.7 (41.7–53.7)		54.5 (44.3–64.3)	43.7 (37.1–50.5)		50.0 (40.4–59.6)	45.7 (39.1–52.5)		47.7 (39.7–55.9)	46.4 (38.8–54.3)	
Poor/very poor	13.6 (3.6–36.0)	8.3 (5.4–12.4)	0.631	10.9 (5.8–19.0)	7.7 (4.7–12.2)	0.057	10.0 (5.2–18.0)	8.1 (5.0–12.7)	0.553	8.4 (4.7–14.2)	8.9 (5.3–14.6)	0.972
Frequency of visits to doctor (during last 12 months; means ± SD	9.2 ± 20.4	6.8 ± 8.8	0.709	7.9 ± 11.3	6.4 ± 9.0	0.080	6.7 ± 6.6	6.9 ± 10.9	0.177	7.6 ± 12.2	6.1 ± 6.8	0.316
Chronic diseases/disability												
Yes, I personally	13.6 (3.6–36.0)	12.7 (9.1–17.3)		20.8 (13.6–30.2)	10.4 (6.9–15.4)		16.0 (9.7–25.0)	12.6 (8.7–17.9)		15.6 (10.4–22.5)	11.9 (7.6–18.0)	
Yes, a person close to me	22.7 (8.7–45.8)	28.6 (23.4–34.4)		30.7 (22.1–40.8)	28.1 (22.3–34.6)		29.0 (20.6–39.1)	28.8 (23.1–35.3)		29.2 (22.3–37.2)	28.6 (22.0–36.1)	
No	63.6 (40.8–82.0)	58.7 (52.6–64.5)	0.855	48.5 (38.5–58.6)	61.5 (54.7–67.9)	0.024	55.0 (44.8–64.9)	58.6 (51.8–65.1)	0.685	55.2 (47.0–63.1)	59.5 (51.7–66.9)	0.579
Mobile phone use												
Yes	71.4 (42.0–90.4)	95.1 (89.8–97.8)		96.8 (88.0–99.4)	91.7 (84.4–95.9)		95.7 (84.3–99.3)	92.7 (86.3–96.4)		93.2 (84.3–97.5)	93.8 (86.5–97.5)	
No	28.6 (9.6–58.0)	4.9 (2.2–10.2)	0.009	3.2 (0.6–12.0)	8.3 (4.1–15.6)	0.332	4.3 (0.7–15.7)	7.3 (3.6–13.7)	0.729	6.8 (2.5–15.7)	6.2 (2.5–13.5)	1

[a]The item related to the education of the respondents included 11 options, from basic to university level, specific to the Polish education system. The 11 levels were collapsed into 3 categories according to the International Standard Classification of Education (ISCED): (A) education level lower than upper secondary; (B) education level including upper secondary to post-secondary non-tertiary; and (C) education level covering all levels according to ISCED higher than post-secondary non-tertiary

Table 4 Factors affecting the attitudes, behaviors, and emotions of citizens 50+ using the Internet for health related purposes; Part 2

Characteristics	Suggestions or queries on diagnosis or treatment to the family doctor, specialists or other health professionals; mean % (CI)	No suggestions or queries on diagnosis or treatment to the family doctor, specialists or other health professionals; mean % (CI)	P-value	Changing of use of medicine without consulting the doctor or other health professionals; mean % (CI)	No change of use of medicine without consulting the doctor or other health professionals; mean % (CI)	P-value	Making, cancelling or changing an appointment with the doctor or other health professionals; mean % (CI)	No making, cancelling or changing an appointment with the doctor or other health professionals; mean % (CI)	P-value
Gender									
Men	50.3 (42.1–58.6)	51.1 (43.5–58.8)		56.0 (35.3–75.0)	50.3 (44.5–56.1)		43.9 (31.9–56.7)	52.5 (46.2–58.7)	
Women	49.7 (41.4–57.9)	48.9 (41.3–56.5)	0.911	44.0 (25.0–64.7)	49.7 (43.9–55.5)	0.679	56.1 (43.4–68.1)	47.5 (41.3–53.8)	0.218
Age (years, means ± SD)	57.8 ± 7.2	58.3 ± 7.0	0.331	59.5 ± 7.5	57.9 ± 7.4	0.249	57.5 ± 7.4	58.2 ± 7.0	0.341
Education[a]:									
A level	22.1 (15.9–29.8)	31 (24.4–38.6)		36.0 (18.7–57.4)	26.2 (21.4–31.6)		33.3 (22.5–46.1)	25.3 (20.2–31.1)	
B level	40.3 (32.4–48.6)	43.1 (35.7–50.8)		44.0 (25.0–64.7)	41.6 (36.0–47.4)		43.9 (31.9–56.7)	41.2 (35.2–47.5)	
C level	37.6 (29.9–45.9)	25.9 (19.7–33.1)	0.050	20.0 (7.6–41.3)	32.2 (27.0–37.9)	0.377	22.7 (13.7–35.0)	33.5 (27.0–39.6)	0.191
Employment status									
Paid work (including self-employment)	45.3 (37.1–53.6)	42.5 (35.1–50.2)		36.0 (18.7–57.4)	44.4 (38.7–50.3)		42.4 (30.6–55.2)	44.1 (38.0–50.5)	
Retired/housework/ care for children or other persons/ unemployed, and others	48.0 (39.8–56.3)	52.3 (44.6–59.9)		60.0 (38.9–78.2)	49.5 (43.7–55.3)		51.5 (39.0–63.9)	50.0 (43.9–56.1)	
Permanently sick or disabled	6.8 (3.5–12.4)	5.2 (2.5–9.9)	0.6612	4.0 (0.2–22.3)	6.1 (3.7–9.6)	0.660	6.1 (2.0–15.6)	5.9 (3.4–9.7)	0.974
Place of residence									
Big cities (above 100,000 residents)	36.9 (29.3–45.2)	32.9 (26.1–40.6)		32.0 (15.7–53.6)	35.0 (29.7–40.8)		39.4 (27.8–52.2)	33.6 (27.9–39.8)	
Minor cities	32.9 (25.5–41.1)	36.4 (29.3–44.1)		44.0 (25.0–64.7)	34.0 (28.7–39.7)		27.3 (17.4–39.8)	36.7 (30.9–43.0)	
Villages/rural area	30.2 (23.1–38.3)	30.6 (24.0–38.2)	0.727	24.0 (10.2–45.5)	31.0 (25.8–36.6)	0.611	33.3 (22.5–46.1)	29.7 (24.2–35.8)	0.361
Type of residence									
Alone	14.9 (7.8–26.2)	8.7 (4.3–16.2)		23.1 (6.2–54)	10.1 (6.1–16.2)		7.1 (1.2–25.0)	11.9 (7.3–18.6)	
With family	85.1 (73.8–92.2)	91.3 (83.8–95.7)	0.221	76.9 (46.0–93.8)	89.9 (83.8–93.9)	0.162	92.9 (75.0–98.8)	88.1 (81.4–92.7)	0.743

Health status (subjective assessment)									
Very good/ good	43.0 (35.0–51.3)	45.4 (37.9–53.1)		32.0 (15.7–53.6)	45.3 (39.6–51.1)		40.9 (29.2–53.7)	45.1 (39.0–51.4)	
Fair	49.0 (40.8–57.3)	45.4 (37.9–53.1)		56.0 (35.3–75.0)	46.3 (40.6–52.1)		51.5 (39.0–63.9)	45.9 (39.7–52.2)	
Poor /very poor	8.1 (4.4–14.0)	9.2 (5.5–14.8)	0.827	12.0 (3.2–32.3)	8.4 (5.6–12.3)	0.398	7.6 (2.8–17.5)	8.9 (5.9–13.3)	0.750
Frequency of visits to doctor (during last 12 months; means ± SD)	6.9 ± 6.9	6.8 ± 11.7	0.127	8.6 ± 6.9	6.7 ± 10.0	0.043	6.8 ± 6.5	6.9 ± 10.5	0.177
Chronic diseases/ disability									
Yes, I personally	14.8 (9.7–21.7)	12.7 (8.3–18.8)		24.0 (10.2–45.5)	12.8 (9.3–17.3)		10.6 (4.7–21.2)	14.5 (10.5–19.5)	
Yes, a person close to me	30.9 (23.7–39.0)	27.2 (20.8–34.5)		20.0 (7.6 4–1.3)	29.6 (24.6–35.2)		30.3 (19.9–43.0)	28.5 (23.2–34.5)	
No	54.4 (46.0–62.5)	60.1 (52.4–67.4)	0.577	56.0 (35.3–75.0)	57.6 (51.7–63.2)	0.231	59.1 (46.3–70.8)	57.0 (50.7–63.1)	0.771
Mobile phone use									
Yes	94.0 (84.7–98.1)	93.3 (86.1–97.0)		92.3 (62.1–99.6)	93.7 (88.4–96.8)		89.3 (70.6–97.2)	94.4 (88.9–97.4)	
No	6.0 (1.9–15.3)	6.7 (3.0–13.9)	1	7.7 (0.4–37.9)	6.3 (3.2–11.6)	0.592	10.7 (2.8–29.4)	5.6 (2.6–11.1)	0.391

[a]The item related to the education of the respondents included 11 options, from basic to university level, specific to the Polish education system. The 11 levels were collapsed into 3 categories according to the International Standard Classification of Education (ISCED): (A) education level lower than upper secondary; (B) education level including upper secondary to post-secondary non-tertiary; and (C) education level covering all levels according to ISCED higher than post-secondary non-tertiary

with a lack of feeling of anxiety, has not been confirmed. There were no significant factors affecting a willingness to change life-style habits, and making, canceling or changing appointment with a doctor. No significant associations were found between the attitudes and behavior of citizens 50+ and other variables, such as employment status, type of residency and subjective assessment of health status.

4 Discussion

Patient use of Internet-acquired health information continues to grow (Pew Internet 2014; Wald et al. 2007; Krane Harris Poll 2006). The study performed by Murray et al. (2003) showed that 85 % of physicians had experienced a situation when a patient had brought information obtained *via* the Internet on a visit; 59 % of them stated that approximately up to one fifth of their patients had done this. The majority of health-related Internet searches by patients are for specific medical conditions and affect an encounter with a doctor. They are carried out by patients for different purposes: (1) before the medical appointment to find information on how to manage their own healthcare independently or decide whether to consult a health professional; (2) to find health information prior to an appointment to be prepared for a medical consultation; and (3) to find information after an appointment with a health professional to assess the consultation, to get a 'second opinion', to be reassured or to expand information received from the doctor (Santana et al. 2011; Wald et al. 2007; Akerkar and Bichile 2004; Ziebland et al. 2004). In our study, more than 70 % of citizens 50+, using the Internet for health purposes, had researched health information that could help them decide whether to consult a health professional, more than half used the Internet to gather health information before a medical encounter, and 64 % had searched for health information to assess the outcome of a medical consultation and obtain a 'second opinion'. Similar, but somewhat lower, results were found by other authors (Andreassen et al. 2007; Krane Harris Poll 2006). According to a Harris Poll, 45–52 % of 'cyberchondriacs' had searched for health information based on a discussion with a doctor in 2005–2006 (Krane Harris Poll 2006). In turn, Rainie and Fox (2000) reported that 61 % of Internet users who sought medical information for themselves, and 73 % of those who sought information for others, turned to Web resources in connection with a visit to the doctor: 55 % of online 'health seekers' gathered online information before a consultation (Akerkar and Bichile 2004; Fox and Rainie 2002), and 50 % were seeking a second opinion from another physician (Akerkar and Bichile 2004; Rainie and Fox 2000). In the present study, the younger group of those surveyed (50–59 years) used the Internet slightly more often for these purposes, and the number of people over 50 in 2012, who had looked online for health information to help deal with a consultation, had significantly increased compared with studies from 2005 to 2007.

Online health information can affect the attitude, emotions, and health behaviors of older Polish citizens in different ways. Using the Internet for health purposes may result in triggering both negative and positive emotions. There is little research specifically exploring emotions that Internet users exhibit during the search process. Web-based patient information may serve to augment the information provided by doctors, and supplemental web information post-visit may help patients feel reassured, more comfortable, and satisfied with the medical consultation and treatment decision (Wald et al. 2007). In spite of its many advantages, the quality of Internet information is highly variable, and health information on the Web may be misleading or misinterpreted by the patients, inducing anxiety and resulting in inappropriate health decisions (Wald et al. 2007; Mc Caw et al. 2007). A few studies have also raised concerns regarding negative emotions, such as increased depression, fear, anxiety, worry and tension after being exposed to online health information (Gadahad et al. 2013). In our study, feelings of reassurance or relief after obtaining information on health or illness were reported by a similar number of respondents as feelings of anxiety and fear.

Among different factors influencing attitudes and behaviors of citizens 50+ using the Internet for health purposes, significantly more feelings of anxiety were reported by women, persons living in rural areas and those suffering from chronic diseases or disability. Analyzing the subsequent surveys, older citizens in 2012 were significantly more frequently afflicted by anxiety caused by using the Internet than citizens in 2005 and 2007, which raises our concern and requires further in-depth observation. The European study of the use of e-health services by citizens, conducted in 2005, showed that it was twice as common for users to feel reassured after accessing the Internet for health purposes as it was to experience anxiety (Andreassen et al. 2007). However, in the Harris Poll in 2006, the percentage of those who indicated that online medical information was 'very reliable' had declined substantially from 37 % in 2005, to 25 % in 2006 (Krane Harris Poll 2006). This also raises anxiety and shows how important an issue the credibility of websites and up-to-date information is.

Willingness to change diet or other life-style habits, or making suggestions or queries on diagnosis or treatment to a doctor, were the most likely effects of health-related use of the Internet. According to the Pew Internet Health Report (Fox and Rainie 2002), 65 % of online health researchers has looked for information concerning nutrition, exercise or weight control. It is such material, as well as information concerning diseases and facts about prescription drugs, which topped the list of their interests (Wald et al. 2007). Our study revealed that almost half of all 50+ citizens were ready for a change of diet or other life-style habits, based on information they had found on the Web. These results were somewhat higher than those of other researchers; Campbell and Nolfi (2005) reported that 39 % of elderly adults were willing to change the way they eat or exercise, as were 33 % of adult Internet users reported by Andreassen et al. (2007). 'Cyberchondriacs' are also found to be using the Internet to assist them in their discussion with their physicians. The Harris Poll found that patients who searched the Internet for health information were more likely to ask more specific and informed questions of their doctors and to comply with recommended treatment plans (Harris Interactive 2001). On the other hand, Ferguson had already reported in 1998 that a third or more of patients were asking their physicians about health information they had found on the Internet, requesting them to recommend the best websites for their conditions, and asking for their e-mail addresses (Ferguson 1998). Various studies report that 28–55 % of those who looked for Internet health information had had a discussion concerning the information with their doctors (Ressi 2011; Bylund et al. 2007; Akerkar and Bichile 2004; Rainie and Fox 2000). Compared to those who did not discuss their Internet health information, those who did have poorer health and rate the quality of information higher (Santana et al. 2011; Bylund et al. 2007). Similar results were obtained in our study, with 46 % of older citizens making suggestions or queries on diagnosis or treatment to a doctor on the basis of information found on the Internet. However, a relationship with health status was not confirmed, and the only significant factor was a high level of education, which positively correlated with the need for discussion with a physician. A worrying phenomenon is, however, the gradual decrease in the need for a conversation with a doctor in subsequent surveys, which was also observed by Krane (Harris Poll 2006).

As was mentioned earlier, the 'e-revolution' has caused a shifting of power within the health care relationship, and e-patients 'empowered' with Web information are much more likely to make decisions and take responsibility for their own health. Many e-patients believe that the medical information and guidance they can find online is more complete and useful than the expertise they receive from their doctors (Ferguson 2004). On the other hand, some physicians may feel that patients are challenging their authority during the visit and experience conflict with more assertive patients (Murray et al. 2003). Moreover, some studies report that online health information negatively influences users' healthcare decisions as wrong self-diagnosis, resulting in their engaging in

treatment options inconsistent with professional recommendations and buying over-the-counter drugs (Gadahad et al. 2013). In our study, more than 20 % of citizens aged 50+ decided to make, change, or cancel an appointment with a doctor as a result of researching online health information, and almost 8 % took a critical decision to change their use of medicines without consulting their family doctor, specialist, or any other health professionals. Comparing the outcomes with the European survey reported by Andreassen et al. (2007) (9 % and 4 %, respectively), our results are higher, and older citizens proved to be less reliant on their providers to make decisions concerning their care. This has also been observed by other researchers (Ressi 2011; Akerkar and Bichile 2004; Rainie and Fox 2000). It is also interesting to note that the only factor significantly related to a more frequent change of use of medicines without consulting a physician or other health professionals, was higher frequency of visits to the doctors. This seems to indicate that patients regularly visiting their physicians are more willing to make independent decisions concerning their health.

5 Conclusions

The Internet has profoundly changed the way patients search for health information. The attitudes, emotions and health behaviors of citizens have all been affected in different ways by information derived *via* the Web. Physicians should be aware of how much influence the Internet and online health information has had on their patients and the resulting risks and benefits. On the one hand, the Internet can empower patients and increase their sense of control over disease by providing patients with the knowledge and self-awareness necessary to make informed decisions about their health and improve the quality of their lives. On the other hand, depending on the source, health information on the web may be misleading or misinterpreted, influencing patients' health behaviors and health outcomes, triggering patient anxiety and other negative emotions, and even resulting in their taking inappropriate decisions with regard to their health or illness.

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Socioeconomic Indicators Shaping Quality of Life and Illness Acceptance in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Quality of life (QoL) combined with the acceptance of illness reflects the efficiency of therapy and the level of patients' satisfaction with medical care. Education, marital status, and place of residence were used as the socio-economic status indicators. The purpose of this study was to determine the relationship between the levels of QoL and acceptance of illness (AI) and the socio-demographic data in patients with chronic obstructive pulmonary disease (COPD). The study involved 264 adult COPD patients. The average duration of COPD was 9 years (Q1–Q3: 3.0–12.0). The duration of the disease was significantly shorter in patients from rural areas. QoL correlated positively with AI ($r = 0.69$, $p < 0.0001$). The general QoL and AI were most strongly influenced by education, gender, and age. Education is a strong predictor of QoL and AI, and the latter correlate with the socioeconomic status of COPD patients. It is recommended that COPD patients with a low level of education have regular medical check-ups and are included in the preventive programs by general practitioners to improve their somatic status and QoL level.

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Keywords
Chronic disease • Family physician • Prevention • Socio-demographic data • Somatic status • WHOQOL-Bref

1 Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory conditions. According to the forecasts of the World Health Organization (WHO), it will be the third leading cause of death in the world, after cardiovascular and neoplastic diseases in 2030 (WHO 2013). There are predictions that COPD will become the seventh cause of disability, expressed as lost disability-adjusted life years (DALYs, and one of the main contributors to chronic morbidity worldwide (GOLD 2013; Nurmatov et al. 2012; Aslani et al. 2007; Mannino and Buist 2007; Ståhl et al. 2005). At present, nearly 40 % of COPD patients are forced to draw sickness benefit (every second patient is younger than 65). These patients die 10–15 years earlier than those without COPD and the emphasis is put on the urgent need for prevention of the disease and research into possible improvements in quality of life (QoL) of COPD patients (Nurmatov et al. 2012; Aslani et al. 2007).

Effective COPD management and prevention strategies include four elements: (1) evaluation and monitoring of disease, (2) reduction of risk factors, (3) stabilization, and (4) treatment of exacerbations (GOLD 2013). In COPD treatment, it is essential to improve QoL and general health. Ståhl et al. (2005) and Ferrer et al. (1998), who measured QoL in patients at various stages of COPD development, found that even those with moderate COPD (FEV1 $>$ 50 % of predicted value) have significantly lower QoL levels. Engström et al. (2001), on the other hand, claim that the worsening of QoL in COPD patients only occurs when the FEV1 drops below 50 % of predicted value.

QoL studies carried out among COPD patients are gaining an increasing importance as a valuable complement to the assessment of the patient's clinical status, effectiveness of therapy, education and prevention, and clinical evaluation of drugs (Bąk-Drabik and Ziora 2010; Maly and Vondra 2006). Prescott and Vestbo (1999) assert that QoL measurement may be used as a good indicator of health status treatment efficiency in COPD patients. WHO defines QoL as individuals' perception of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns. The QoL level and health status in chronic conditions are measured by both general and disease-specific questionnaires.

COPD as a chronic illness has effects on social, psychological, and economic spheres of life. Maly and Vondra (2006) maintain that the use of general and disease-specific questionnaires together is probably the best approach to the evaluation of QoL and health status. Bąk-Drabik and Ziora (2010) demonstrated that QoL in COPD patients is lower than in the healthy population and it is particularly influenced by socioeconomic factors; the element being so far poorly described. Similar conclusions were drawn by Prescott and Vestbo (1999). In their opinion, even patients with mild COPD are not satisfied with their QoL which is adversely influenced by physical and psychological consequences of respiratory disease, including sleep disorders, low effort tolerance, and limited possibility of doing everyday activities.

Socioeconomic status refers to the position of an individual in the society, which is mainly conditioned by education (Krieger et al. 1997; Laurent et al. 2008; Bacon et al. 2009), income, professional activity, and actual profession (Braveman et al. 2005). The level of education is often used as a main socioeconomic status indicator, because it is steady over time, whereas

profession and income may change during a lifespan. Krieger et al. (1997) found that respondents were more eager to answer questions about education than questions about income, which often were left unanswered.

The living environment is also an important indicator of socioeconomic status. There is evidence for the fact that health differences may depend on income, wealth, education, profession, and the socioeconomic features of the environment. Therefore, it seems sensible to analyze the influence of separate socioeconomic factors rather than general socioeconomic status (Braveman et al. 2005). Furthermore, O'Malley et al. (2007) and Bacon et al. (2009) indicate the necessity of considering socioeconomic status as a variable in QoL measurement. According to these authors, low socioeconomic status is associated with higher morbidity and mortality rates due to chronic diseases, including cardiovascular conditions, COPD, asthma and diabetes (Bacon et al. 2009; O'Malley et al. 2007). Braveman et al. (2005) prove that both in clinical and public health research, socioeconomic status is usually treated as a control variable, and less frequently as a response variable, which may have effects on the research results and their implications for health practice and health policy.

Socioeconomic status seems to play a more important role in COPD than in other chronic diseases (Shavro et al. 2012). On the individual level (professional, social and economic status, education, and income per capita), low status may cause higher exposure both to harmful factors at home (indoor exposure, e.g. cockroach, dust, cigarette smoke, or mycotic fungi) and outside of it (outdoor exposure, e.g. the environmental pollution or not taking drugs because of high costs of treatment). Consequently, low socioeconomic level increases the risk of COPD exacerbations (Shavro et al. 2012; Laurent et al. 2008; Aslani et al. 2007). The knowledge of the relationship between COPD and particular socioeconomic elements is still insufficient, hence the need for research in this field.

An element that should be included in the research on QoL and health status in patients with chronic diseases is the measurement of the acceptance of illness (AI) as a sign of adaptation to limitations and disability caused by the disease (Juczynski 2009). High AI leads to a reduction of negative emotions associated with a chronic disease and its therapy. According to Nowicki and Ostrowska (2008), adaptation to the disease, manifested as acceptance of illness, plays an important role in the control, including self-control of chronic diseases. AI modulates QoL: high AI level contributes to higher QoL, obedience to doctor's orders, and coping better with disease-related limitations. There is evidence of some regularities in the influence on AI of socioeconomic status, which refers to socio-demographic and economic variables; notably the level of education and the place of residence (Kaczmarczyk 2010; Bacon et al. 2009; O'Malley et al. 2007; Krieger et al. 1997).

The purpose of this study, was to establish how the QoL and AI levels are related to socioeconomic status of adult COPD patients. It was assumed that socio-economic status might correlate with both QoL and AI. Furthermore, the influence of socioeconomic variables on health care utilization was taken into account in the analysis.

2 Methods

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and was approved by the Bioethical Commission of Wroclaw Medical University (no. KB 608/2011). The main inclusion criteria were: minimum 18 years of age, COPD diagnosis, and written consent of patients to participate in the study.

The study included 264 COPD patients, mean age of 60.2 $\pm$ 13.2 years, who were under care of 34 family doctors in Poland. Detailed socio-demographic data of the patients are shown in Table 1. The questionnaire was completed in the presence of the project executors; current spirometry results were attached to questionnaires.

Table 1 Sociodemographic data of COPD patients (n = 263)

	n	%	Mean ± SD Q1–Q3	Chi^2 p
Gender				
Women	123	46.8		1.1
Men	140	53.2		0.29
Age				
24 and below	4	1.5		
25–44	20	7.6	60.2 ± 13.2	298.7
45–64	151	57.6	53.0–70.0	<0.0001
65–84	78	29.8		
85 and above	9	3.4		
Place of residence				
Village	136	51.7		
Below 5,000*	56	21.3		
5,000–10,000*	7	2.6		466.1
10,000–50,000*	35	13.3		<0.0001
50,000–100,000*	19	7.2		
100,000–200,000*	4	1.5		
Over 200,000*	6	2.3		
Education				
Incomplete primary – below 8 years	1	0.4		
Primary – 8 years	60	22.8		336.2
Vocational – 10 years	85	32.3		<0.0001
Secondary – 12 or 14 years	96	36.5		
Higher – 17 or above 17 years	21	8.0		
Marital status				
Single	21	8.0		
Married	185	70.3		431.0
Separated	4	1.5		<0.0001
Divorced	12	4.6		
Widowed	41	15.6		
Smoking				
Non-smokers	75	28.4		
Smokers	53	20.1		

*Town/city population

The QoL profile was investigated with the Polish version of the World Health Organization Quality of Life Instrument Short Form (WHOQOL-BREF). This is an instrument which conceptually derives from the QoL definition proposed by WHO. It contains 26 questions, the two first of which provide information on how individuals perceive their health and general quality of life. Other questions evaluate four QoL domains: physical, psychological, social relationships, and environmental (Wolowicka and Jaracz 2001; WHOQOL Group 1998).

The answers to all WHOQOL-BREF questions, including the first two concerning the satisfaction with QoL and health status, are weighed on a five point Likert-type scale, ranging from 1- 'does not occur at all' to 5 – 'it does occur'. A maximum of 5 points could be obtained for questions 1 and 2, 4–20 points for each domain. The total QoL score is the

arithmetic sum of the scores obtained in the four WHOQOL-BREF domains: the higher the score, the higher the QoL level. The final results were interpreted as follows: the score $\geq$ 75 % of the total score = very high QOL, 50–74.9 % = high QOL, and <50 % = low QoL. The reliability of the WHOQOL-BREF Polish version, measured with the α-Cronbach coefficient, is in a range of 0.81–0.69 for individual domains and 0.90 for the whole questionnaire.

The AI was investigated with the Acceptance of Illness Scale consisting of eight questions about consequences of bad health status. The questions concerned limitations caused by disease, lack of self-sufficiency, feeling of dependence on others, and low self-esteem. Each question was weighed on a five point Likert-type scale. Resolute agreement with a particular statement corresponded with the weak adaptation to disease (1 point), while resolute disagreement indicated acceptance of illness (5 points). The possible score ranged from 8 to 40 points and reflected the degree of general acceptance of disease. A low score (8–18 points) denoted lack of acceptance and adaptation as well as a strong feeling of psychological discomfort. A high score (30–40 points) suggested acceptance of disease together with lack of negative emotions associated with it. A score of 19–29 demonstrated that the patient had managed to partially adapt to disease. The α-Cronbach coefficient of the Polish version of the scale is 0.85 (Nowicki and Ostrowska 2008).

The socioeconomic measure was based on the patients' answers concerning the education defined by the number of schooling years (Laurent et al. 2008; Krieger et al. 1997), place of residence, marital status, gender, and age. Lung function was assessed from the forced expired volume in 1 s (FEV1) measurements taken during the preceding year, expressed in percent predicted values.

To unify the results, a somatic index was used in the study. Somatic symptoms reported by the patients were assigned to values from one (symptoms occurring once a year) to seven (permanent symptoms). The index was calculated by summing up values assigned to somatic symptoms and then dividing this sum by 49 (the highest possible score).

Means ± SD, medians, min-max values were calculated for measurable (quantitative) variables, while for qualitative variables the frequency (percentage) was determined. Spearman's rank correlation coefficient was used to assess associations between variables. Data were not normally distributed as assessed with the Shapiro-Wilk test. Analysis of logistic regression was used to examine the impact of explanatory variables on QoL and AI levels. The critical level of significance was assumed at $p < 0.05$. Statistical analysis was performed using R2.10.1 (for Mac OS X Cocoa GUI).

3 Results

The mean age of rural patients was higher than that of urban patients (63.5 ± 11.8 *vs.* 56.6 ± 14.1 years, $p < 0.0001$). There were also significant differences in the percentage of the post-working age population between urban and rural areas: the percentage of people aged 65–85 years or more was higher in rural than urban areas – 40.0 % (54 persons) and 26.0 % (33 persons), respectively ($p = 0.002$).

The level of education depended on the place of residence ($p \leq 0.001$). In rural areas, the percentage of patients with primary education was higher than in urban areas (35.3 %, 48 persons and 9.4 %, 12 persons, respectively). Furthermore, patients with vocational education were more numerous in rural areas (39.7 %, 54 persons and 24.4 %, 31 persons, respectively). More urban residents had secondary education (52.7 %, 67 persons and 21.3 %, persons) and higher education (8.6 %, 11 persons and 7.4 %, 10 persons, respectively) than was the case in rural areas.

The patients suffered from COPD for 9.0 ± 6.0 years (range 2.0–35.0 years). The duration of the disease was significantly shorter in rural (8.4 ± 5.3 years) than urban areas (13.4 ± 7.6 years, $p < 0.0001$). The severity of COPD was determined on the basis of spirometry. A mild form of the disease (A) was

Table 2 Quality of life according to the WHOQOL-BREF questionnaire and acceptance of illness according to Acceptance of Illness Scale

QoL domains and AI	n	M	SD	Q.25 %	Q.50 %	Q.75 %	Min	Max
Satisfaction with QoL	263	3.4	0.8	3.0	4.0	4.0	1.0	5.0
Satisfaction with health status	264	2.9	0.9	2.0	3.0	4.0	1.0	5.0
D1 – Physical domain	264	13.1	2.9	11.4	13.1	15.4	4.6	19.4
D2 – Psychological domain	264	13.0	2.8	10.6	12.6	15.3	6.6	18.6
D3 – Social relationships domain	264	14.2	2.8	12.0	14.6	16.0	6.6	20.0
D4 – Environmental domain	263	13.4	2.4	12.0	13.5	15.0	7.0	18.5
Total QoL	263	53.8	9.8	47.2	52.2	60.0	29.1	76.6
AI	258	25.9	6.9	21.0	25.0	31.0	8.0	40.0

QoL quality of life, *AI* acceptance of illness, *M* mean, *SD* standard deviation, *Q* quartile

diagnosed in 53.4 % (141 patients), moderate (B) in 36.4 % (96 patients), and severe (C) in 1.1 % (3 patients). Less than every tenth patient (9.1 %, 24 patients) had no spirometry done in the year preceding the study. Most patients (28.0 %, 74 persons) reported three diseases, (25.8 %, 68 persons) two diseases, and 47 (17.8 %, 47 persons) four diseases. The average number of diseases was 3.2 ± 1.6 (range 1–9 diseases).

The average value of the somatic index was 0.4 ± 0.2. Somatic improvement during the previous 12 months was reported by 37.8 % of patients (100 persons) and psychological improvement by 40.2 % of patients (106 persons) ($p > 0.05$). There were no significant differences in the index of health services between residents of urban and rural areas ($p = 0.06$). During the 12 months prior to the study, the average number of health services was 5.2 ± 5.2 (range 0–30).

Patients' overall satisfaction with QoL was at a reasonably good level (3.5 ± 0.9). However, patients were dissatisfied with their health status; the average score being 2.9 ± 0.9 (Table 2). Patients with higher education were more satisfied with QoL and health status ($Chi^2 = 34.4$, $p < 0.0001$ and $Chi^2 = 34.1$, $p < 0.0001$, respectively).

There were differences in satisfaction with QoL and health status measured with reference to the indicators of socioeconomic status. Patients with higher education had higher QoL than those worse educated ($Chi^2 = 34.4$, $p < 0.0001$), younger patients had higher QoL than older ones ($Chi^2 = 34.4$, $p < 0.0001$), and patients from towns/cities with a population of over 50,000 had higher QoL than those from rural areas and towns/cities with a population up to 2,000 ($Chi^2 = 18.1$, $p = 0.02$). Satisfaction with health status depended on education ($Chi^2 = 34.1$, $p < 0.0001$), age ($Chi^2 = 20.5$, $p < 0.001$), and gender ($Chi^2 = 5.2$, $p = 0.02$).

The overall QoL score was 53.8 ± 9.8, which implied very good and good QoL. The social relationships domain scored high (14.2 ± 2.8) and the psychological domain scored low (13.0 ± 2.8), while in the physical and environmental domains the results were similar. There were statistically significant differences in QoL depending on education, age, and place of residence; very good QoL was observed in patients with education of 14 years of schooling or more, patients aged up to 44 years, and residents of towns and cities ($Chi^2 = 104.5$, $p < 0.0001$).

There were significant QoL differences in the physical domain depending on education, age, and gender ($Chi^2 = 93.4$, $p < 0.0001$). In this domain, QoL was more often assessed as very good in patients with higher education, younger patients, and in women. Worse QoL (score below 13.99 points) was noted in poorly educated and older patients, and men ($Chi^2 = 93.4$, $p < 0.0001$). QoL also differed in the social relationships domain, depending on education, age, and the place of residence ($Chi^2 = 88.5$, $p < 0.0001$). Patients with higher education, younger patients, and rural residents evaluated QoL in this domain as very good and good. In the environmental domain, QoL depended on education, age, the place of residence, and

gender ($Chi^2 = 107.2$, $p < 0.0001$). QoL was more often assessed as very good and good by well-educated and younger patients, residents of towns/cities, and by women.

The average AI result amounted to 25.9 ± 6.9, which may suggest problems with adaptation to life with the disease, a feeling of discomfort, and self-care difficulties among COPD patients. There were significant differences in AI depending on education, the place of residence, age, and gender ($Chi^2 = 70.20$, $p < 0.0001$). Patients with higher education, patients aged up to 44 years, urban patients, and women were prone to better accept their health status.

3.1 Correlations Between Quality of Life or Acceptance of Illness and Socioeconomic Variables

Residents of rural areas were worse educated than those of towns and cities ($r = -0.48$, $p < 0.001$). Unmarried women and men were better educated than widows and widowers ($r = -0.17$, $p = 0.005$), and older patients were better educated than younger ones ($r = -0.46$, $p < 0.0001$). Widows and widowers were older than unmarried women and men ($r = 0.34$, $p < 0.0001$).

QoL of patients correlated with all socioeconomic variables considered in this study. Better educated patients (17 years of schooling or more) assessed their QoL higher than those with primary and incomplete primary education (up to 8 years of schooling) ($r = 0.45$, $p < 0.0001$). Women had higher QoL levels than men ($r = 0.13$, $p = 0.03$). QoL correlated negatively with such variables as marital status, place of residence and age (Table 3). Lower QoL was noted in widows and widowers rather than unmarried women and men ($r = -0.12$, $p < 0.04$), in residents of rural areas rather than those of towns and cities with a population of over 200,000 ($r = -0.24$, $p < 0.0001$), and in older patients rather than younger ones ($r = -0.41$, $p < 0.0001$). There were no significant differences in QoL between smokers and non-smokers ($r = 0.11$, $p = 0.5$).

QoL correlated with satisfaction with QoL ($r = 0.72$, $p < 0.0001$) and health satisfaction ($r = 0.63$, $p < 0.0001$). The satisfaction with QoL also correlated with education, age, and place of residence. The QoL scores in physical, psychological, and social relationships, together with environmental domains, correlated with the levels of satisfaction with QoL and health status: higher QoL in these four domains were accompanied by higher satisfaction with QoL and health status (Table 3).

QoL correlated positively with the AI levels ($r = 0.69$, $p < 0.0001$). The AI levels correlated with the satisfaction with QoL ($r = 0.55$, $p < 0.0001$) and health satisfaction ($r = 0.51$, $p < 0.0001$). The lowest AI was observed among patients whose education was shorter than 12 years, those who lived in rural areas (*vs.* patients from towns/cities with a population of over 200,000) ($r = -0.26$, $p < 0.0001$), and in older patients (*vs.* younger patients) ($r = -0.36$, $p < 0.0001$). Women had higher AI than men ($r = 0.16$, $p = 0.01$), and patients with higher education had higher AI than those with incomplete primary education ($r = 0.36$, $p < 0.0001$).

QoL and AI levels correlated negatively with the number of: health services received during visits to a family doctor (respectively, $r = -0.37$, $p < 0.0001$ and $r = -0.23$, $p = 0.005$), home visits ($r = -0.30$, $p = 0.001$ and $r = -0.29$, $p = 0.001$), consultations by phone ($r = -0.22$, $p = 0.008$, $r = -0.22$, $p = 0.007$), and interventions of a district nurse during the previous 12 months ($r = -0.30$, $p = 0.001$ and $r = -0.29$, $p = 0.001$). The somatic index and the index of health services correlated negatively with satisfaction with QoL and health status (respectively, $r = -0.39$, $p < 0.0001$ and $r = -0.30$, $p = 0.001$).

3.2 Correlations Between Socioeconomic Variables and Primary Health Care Utilization

Primary health care utilization significantly correlated with the level of education, place of

Table 3 Correlations between SES and the levels of QOL and AI

	QoL		AI		WB1		WB2	
Variables	r	p	r	p	r	p	r	p
Gender	0.13	0.030	0.16	0.010	0.06	0.320	0.14	0.020
Age	−0.41	<0.0001	−0.40	<0.0001	−0.28	<0.001	−0.24	<0.001
Education	0.45	<0.0001	0.36	<0.0001	0.32	<0.001	0.25	<0.001
Marital status	−0.12	0.040	−0.11	0.080	0.42	0.710	−0.02	0.690
Place of residence	−0.24	<0.0001	−0.26	<0.0001	−0.15	0.020	−0.08	0.180
Total QoL	–	–	0.69	<0.0001	0.72	<0.0001	0.63	<0.0001
AI	0.69	<0.0001	–	–	0.55	<0.0001	0.51	<0.0001

SES socioeconomic status, *QoL* quality of life, *AI* acceptance of illness, *r* Spearman's rank correlation coefficient, *WB1* satisfaction with QoL, *WB2* satisfaction with health status

residence, and age of COPD patients, and did not correlate with gender and marital status. The lower the education, the more patients made use of visits to a family doctor ($r = -0.26$, $p = 0.002$), home visits ($r = -0.26$, $p = 0.001$), consultations by phone ($r = -0.25$, $p = 0.002$), and interventions of a district nurse ($r = -0.55$, $p < 0.0001$). Residents of rural areas more often made use of: visits to a family doctor ($r = 0.24$, $p = 0.003$), home visits ($r = 0.31$, $p < 0.001$), consultations by phone ($r = 0.22$, $p = 0.007$), and interventions of a district nurse ($r = 0.53$, $p < 0.0001$) than those of towns/cities with a population of over 200,000.

Patients aged over 65 years of age had more frequent visits to a family doctor ($r = 0.31$, $p = 0.0002$), home visits ($r = 0.39$, $p < 0.0001$), consultations by phone ($r = 0.32$, $p < 0.0001$), and interventions of a district nurse ($r = 0.44$, $p < 0.0001$) than younger patients. The number of spirometry tests performed during the previous 12 months correlated negatively with the number of hospitalizations ($r = -0.28$, $p < 0.0001$) and with the number of visits to a family doctor ($r = -0.59$, $p < 0.0001$).

3.3 Quality of Life and Acceptance of Illness *vs.* Socio-demographic Variables

The logistic regression results are shown in Table 4. The general QoL level was most strongly influenced by education, gender, age, and the place of residence. The odds ratio (OR) of a high QoL level was 74 times higher in patients with higher education than in those with primary or incomplete primary education (OR = 73.8; 95 % CI: 19.4–628.4); 2.5 times higher in patients aged 50 than those aged 70 (OR = 2.5, 95 % CI: 1.1–6.1); and almost twice as high in women as in men (OR = 1.8; 95 % CI: 1.2–2.6). Place of residence contributed to QoL level: residents of the biggest towns/cities had 3 times higher OR of the high QoL level than rural residents (OR = 2.93; 95 % CI: 1.98–4.36).

Education ($p = 0.008$), gender ($p = 0.02$), and age ($p < 0.0001$) had the strongest impact on the level of AI levels. The odds ratio of high AI levels was 39 times higher in patients with higher education than in those with primary or incomplete primary education (OR = 39.5, 95 % CI: 14.5–150.6) and twice higher in patients aged 50 years than in those aged 70 years (OR = 2.3, 95 % CI: 1.1–5.3).

4 Discussion

This study describes the influence of sociodemographic data on quality of life and acceptance of illness in a cohort of Polish adults suffering from COPD. A variable accepted as an indicator of socioeconomic status was the level of education determined by the number of years of completed education (OECD 2013; Bąk-Drabik and Ziora 2010; Bacon et al. 2009; Braveman et al. 2005). It has been shown that a higher education level results in a longer life span and higher life satisfaction in both women

Table 4 Results of logistic regression ($n = 264$)

	Constant/variables	Estimate β_i	SE	z value	Pr(>|z|)
1	Gender	0.57	0.25	2.24	0.02
3	Education	0.56	0.11	5.26	<0.001
5	Age	−0.04	0.01	−6.10	<0.001
2	Marital status	−0.21	0.10	−2.03	0.040
3	Education	0.45	0.08	5.26	<0.001
4	Place of residence	−0.13	0.04	−3.33	<0.001
1	Gender	0.49	0.16	2.19	0.004
2	Marital status	−0.27	0.09	−2.92	0.003
1	Gender	−0.48	0.18	−2.63	0.008
3	Education	0.25	0.07	3.25	0.001
1	Gender	0.71	0.19	3.62	<0.001
4	Place of residence	−0.14	0.04	−3.68	<0.001
1	Gender	1.06	0.22	4.80	<0.0001
2	Age	−0.02	0.005	−4.89	<0.0001
2	Marital status	−0.38	0.08	−4.29	<0.001
3	Education	0.30	0.06	4.64	<0.001
3	Education	0.39	0.07	5.00	<0.001
4	Place of residence	−0.17	0.03	−4.95	<0.001
3	Education	0.63	0.10	6.11	<0.001
5	Age	−0.03	0.01	−6.14	<0.001
1	Gender	0.58	0.25	2.29	0.020
3	Education	0.46	0.10	4.51	<0.001
5	Age	−0.04	0.01	−5.89	<0.001
1	Gender	0.75	0.19	3.79	<0.001
4	Place of residence	−0.16	0. 0.04	−4.17	<0.001
1	Gender	−0.43	0.18	−2.36	0.018
3	Education	0.20	0.07	2.64	0.008
1	Gender	1.03	0.22	4.64	<0.001
5	Age	−0.02	0.005	−4.94	<0.001
2	Marital status	−0.29	0.08	−3.46	<0.001
3	Education	0.22	0.06	3.53	<0.001
2	Marital status	0.23	0.11	2.08	0.040
5	Age	−0.01	0.005	−2.68	0.001
3	Education	0.36	0.08	4.74	<0.001
4	Place of residence	−0.18	0.04	−5.06	<0.001
3	Education	0.54	0.09	5.58	<0.001
5	Age	−0.03	0.005	−5.84	<0.001

Response variables: quality of life (QoL) and acceptance of illness (AI)

Models: QoL – 1, 2 and AI – 1 are models with three explanatory variables selected from the set of five variables; QoL – from 3 to 9 and AI from 2 to 8 are models with two explanatory variables selected from the set of five variables; Estimate β_i – estimated coefficient β_i in the regression equation; SE – estimated standard error of coefficient β_i; z-value – value of normal reference distribution; Pr(>|z|) – two-tailed p-value corresponding to the z-value

and men (OECD 2013). It is believed that low socioeconomic status may influence health through lifestyle, adverse effects of the living environment, and limited access to health services. On the other hand, education has a substantial influence on patients' ability to take care of themselves (Aslani et al. 2007). Low education is related to poorer control of disease

and worse assessment of self-care efficiency, and higher health care utilization (Bacon et al. 2009).

Higher education is a factor which has the largest positive contribution to quality of life and acceptance of illness in COPD patients. A substantial role of education may stem from the fact that better educated people have better chances to find and keep well-paid jobs. The better educated also know better how to cope with disease-related limitations and search for help. These aspects have also been noticed by Ståhl et al. (2005), Bąk-Drabik and Ziora (2010), and Braveman et al. (2005). In contrast, a low level of education is associated with low health awareness and little knowledge of disease. It is estimated that in Poland about 80 % of COPD patients know nothing much about their condition.

Yin et al. (2011) have found a relationship between the occurrence of COPD in urban and rural areas and socioeconomic status defined by the level of education and income in a household. Low income was associated with low education and a higher incidence of COPD in urban areas; such a relationship is not observed in rural areas. Other studies confirm that a low level of education appreciably contributes to low quality of life, especially in the physical domain (Shavro et al. 2012; Aslani et al. 2007).

In the present study we found that other factors having a strong positive influence on quality of life and acceptance of illness in COPD patients were female gender and younger age. Patients aged over 70 reported a lowering of quality of life and the lack of illness acceptance more often than those aged 50 or less. Similar results were obtained by Engström et al. (2001) and Kaczmarczyk (2010). However, we failed to confirm that marital status is a factor contributing to quality of life and acceptance of illness.

According to Shavro et al. (2012), QoL studies provide detailed information on problems faced by COPD patients, thus enabling medical staff to improve care. The present findings suggest that COPD patients have, on average, very good (over 75 % of total score) or good QoL score (75–50 % of total score), alongside however a with low AI score. It was observed that COPD patients assessed satisfaction with life higher than satisfaction with health status. The difference may due to the natural tendency to assess QoL higher, even when someone suffers from a severe intractable disease. A low assessment of the ability to cope with the disease and limitations in everyday functioning may stem from the feeling of threat to life caused by dyspnea and other respiratory symptoms. Shavro et al. (2012), who have analyzed patients with pain, concluded that those who believe they could control pain do not feel their lives are endangered, are not limited in everyday activities, have higher AI levels, and function better, than those who perceive a threat to life and see themselves as being disabled. Patients with COPD assessed their QoL lowest in the psychological domain. However, in the study of Bąk-Drabik and Ziora (2010) QoL was lowest in the physical domain.

The present study lends support to those other studies which show that a low level of education and low economic status increase health care utilization (Bąk-Drabikand Ziora 2010; Aslani et al. 2007). Worse educated patients, having less than 8 years of schooling, more often made use of: visits to a family doctor, home visits, consultations by phone, and interventions of a district nurse. We also demonstrated that acceptance of illness in COPD patients correlated negatively with the number of home visits and consultations by phone. Those patients with low acceptance of illness used these services more often. Bacon et al. (2009), on the other hand, has demonstrated that an increase in the number of home visits and hospitalizations is associated with the duration of disease and the incidence of its severe form, and not with sociodemographic data.

The present findings demonstrate that a higher number of spirometry tests performed during the preceding 12 months was accompanied by a lower number of hospitalizations and visits to a family doctor. In Poland, more frequent spirometry tests involve more frequent visits to pulmonologists, which suggests that

intensification of care provided for COPD patients reduces the number of hospitalizations and therefore direct medical costs.

The present study has got certain methodological limitations. We did not consider the potential interaction between environmental variables, such as exposure to irritants and air pollution or living conditions, and socioeconomic status, which is pointed to by other authors (Li et al. 2008; Grochans et al. 2012). We also assumed that the level of education defines the patient's socioeconomic status. Other authors use more complex measures of this status, which include income, profession, marital status, age, gender, or others (Krieger et al. 1997). It seems dubious that broadening the scope of socioeconomic indicators could make the results more straightforward. Therefore, we believe that the results of this study complement and reinforce previous reports of the relationship between socioeconomic status and COPD.

Summing up, COPD patients with lower education and socioeconomic status, of male gender, and older age, and residents of rural areas and towns with a population below 5,000 are likely to have lower quality of life and acceptance of illness. The present study could not clearly establish the cause-and-effect relationship between quality of life or acceptance of illness and the variables above outlined. Nevertheless, monitoring of the influence of sociodemographic features on health status and well-being becomes part of taking care of COPD patients and of the evaluation of treatment benefits. In accordance with the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2013), the treatment of COPD should be more individualized and tailored to the needs of each patient.

Conflicts of Interests The authors declare no conflicts of interest in relation to this article.

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Field Safety Notes in Product Problems of Medical Devices for Use in Pulmonology

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Abstract

The current European system for medical devices is governed by three EC directives: the Medical Device Directive 93/42/EEC, the In-Vitro Diagnostic Directive 98/79/EC and the Active Implantable Medical Device Directive 90/385/EEC and regulates marketing and post-market surveillance of medical devices in the European Economic Area. In cases of incidents and field safety corrective actions (FSCA) manufacturers have to inform the responsible Competent Authority, which is the Federal Institute for Drugs and Medical Devices (BfArM) and the public by field safety notices (FSN). In this study we analyzed FSN of medical devices exclusively serving for diagnostics or treatment in pulmonology (e.g. nebulizers, oxygen concentrators, pulse oximeters, lung function analyzers, and non-active devices for treatment). FSCA and FSN publicized by BfArM in 2005–2013 were analyzed in respect to the MEDDEV 2.12-1 rev 8. In total 41 FSCA were publicized for the included products. German and English FSN were found in 36/35 cases, respectively. FSN were clearly characterized as FSN in 22/20 cases and declaration of the type of action was found in 27/26 cases, respectively. Product names were provided in all cases. Lot numbers or other information for product characterization were available in 7/8 and 26/24 cases, respectively. Detailed information regarding FSCA and product malfunction were found in 27/33 and 36/35 cases, respectively. Information on product related risks with previous use of the affected product was provided in 24/23 cases. In 34/34 cases manufacturers provided information to

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mitigate product related risks. Requests to pass FSN to persons needing awareness were found in 10/14 cases. Contact data were provided in 30/30 cases. Confirmation that the Competent Authority was informed was found in 12/14 cases and in 19/18 cases a customer confirmation was included. The obtained data suggest that there is an increasing annual number of FSCA and most FSN fulfill the criteria of MEDDEV 2.12-1 rev 8. However, there are differences between German and English FSN, e.g. regarding the distribution to persons needing awareness, missing statement that the Competent Authority was informed and missing customer confirmation. Due to the importance of FSN for reduction of product related risks in FSCA type and content of FSN should be further improved.

Keywords
Competent Authority • Field safety corrective actions • Market surveillance • Medical devices • Pneumology • Product failure

1 Introduction

The European Council Directive 93/42/EEC (1993) amended in 2007 (Directive 2007/47/EC of the European Parliament 2007) regulates conformity assessment, marketing and post marketing surveillance of medical devices in Europe. The substance of the European Directive has been implemented in Germany by means of the German Law on Medical Devices (MPG, Medizinproduktegesetz) in 1994 and was subject of several amendments later on (Gesetz über Medizinprodukte 1994, 2002). The latter has been flanked by the Ordinance on the Medical Devices Vigilance System (MPSV, Medizinproduktesicherheitsplanverordnung) from 24 June 2002 with later revisions (Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002).

In brief, manufacturers shall be obliged to systematically review the experience gained from devices on the market, to implement corrective actions, where necessary and to report incidents and recalls to the responsible Competent Authority. According to the Ordinance on the Medical Devices Vigilance System, in Germany also professional operators and users have to report to the Competent Authority the incidents that they observe when using products (Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002; Guidelines on a Medical Devices Vigilance System 2013; Medical Devices Post Market Surveillance 2006). The same obligation applies to pharmacies and other retail traders if they notice incidents related to Over the Counter OTC-products sold by them to lay people. In Germany the Federal Institute for Drugs and Medical Devices (BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte) is responsible for registration and examination of issues related to medical devices except a few special *in vitro* diagnostics (IVD) serving for infection testing, immune hematological diagnostics, and tissue-typing as specified in Annex II of Directive 98/79/EC of the European Parliament (1998).

In evaluating the reports or other relevant information regarding risks the task of the Competent Authority is to characterize the risk (concerning likeliness of occurrence of harm and severity of the harm) and to assess it for acceptability. In case of unacceptable risks the necessary corrective action is to be determined. If manufacturers have already taken measures in their own responsibility, the Competent Authority has to take a decision on whether or not these are adequate. Any necessary field safety corrective action (FSCA) performed by the

manufacturers must be properly communicated to the customers and users. In Germany this is typically done by contemporary sending of field safety notes (FSN) . The FSN must also be sent to the BfArM for information and for publication on the homepage of this Competent Authority. In cases of FSCA a brief information regarding the affected product and the corresponding FSN is publicized on the BfArM homepage (2014).

CE-marked (Conformité Européenne) devices in principle enjoy free movement in the entire European Economic Area. Therefore, there is a need for information to be exchanged between Competent Authorities, in particular when an FSCA is to be taken. According the Directive European Competent Authorities inform each other and the European Commission by means of national Competent Authority reports in cases that lead to corrective actions. After being informed all Competent Authorities can monitor the corrective action in their area of responsibility and also consider whether similar products of other manufacturers may also be affected by the observed problem.

Even though Directive 93/42/EEC concerning Medical Devices (1993) and German Law on Medical Devices have been implemented 20 years ago (Gesetz über Medizinprodukte 1994) and IVD were included into European and national regulation only about 5 years later (Directive 98/79/EC of the European Parliament 1998), there are only few data regarding the experience on market surveillance reflecting specific medical devices except IVD (Halbauer et al. 2009; Siekmeier and Lütz 2007a, b; Siekmeier et al. 2008; Spitzenberger et al. 2007).

Large differences in respect to causes of product failure and consecutive risks for patients and users were reported before within the group of IVD (e.g., IVD for lay use *vs*. IVD for professional use, analyzers *vs*. tests, reagents, control materials, calibrators and microbiological growth media, IVD for use in clinical chemistry, hematology, coagulation diagnostics or infection testing) (Siekmeier and Lütz 2007a, b; Siekmeier et al. 2008; Siekmeier and Wetzel 2013a, b). There are also large differences between different groups of medical devices (e.g., active *vs*. non-active medical devices, implantable *vs*. - non-implantable medical devices, medical devices for professional use *vs*. medical devices for lay use) and it is likely that there are also relevant differences between different product groups in respect to product-related risk in cases of product failure, figures of product failure and underlying root-causes of product failure. Therefore, product specific analyzes should be made which may help to identify product specific risks and may serve for further risk reduction. FSN play a central role for risk reduction in cases of product failure related to products already in the market. However, up to now there are little data analyzing the quality of FSN sent by the manufacturers in case of an FSCA even though requirements for FSN are described in MEDDEV 2.12-1 rev 8 (Siekmeier et al. 2010; Guidelines on a Medical Devices Vigilance System 2013; Hannig and Siekmeier 2015). Therefore, aim of this study was the analysis of FSCA and FSN of medical devices serving for diagnostics or treatment in pulmonology in respect to the criteria of MEDDEV 2.12-1 rev 8.

2 Methods

All notifications on medical devices received by the BfArM between the beginning of 2005 and end of 2013 were included in the study as there is no relevant number of publications of FSCA on the BfArM homepage before 2005. Detailed analysis was made for devices exclusively serving for diagnostics or treatment in pulmonology (i.e., active medical devices (nebulizers, oxygen concentrators, pulse oximeters, and lung function analyzers) and non-active medical devices (e.g., devices serving for pleural drainage or treatment of lung emphysema or bronchial stenosis). Other medical devices, e.g., devices for use in otorhinolaryngology and intensive care medicine (e.g., respirators, masks, tracheal tubes and tracheostomae, and materials for bronchial drainage) were excluded from this analysis as those products are more frequently used by other clinicians than by pulmonologists. IVD (e.g., analyzers, consumables and reagents for blood

Table 1 Required content of the field safety notice (FSN) according the guideline MEDDEV 2.12-1 rev 8

1	A clear title, with "Urgent field safety notice" followed by the commercial name of the affected product, an FSCA-identifier (e.g., date) and the type of action.
2	Specific details to enable the affected product to be easily identified e.g. type of device, model name and number, batch/lot or serial numbers of affected devices and part or order number.
3	A factual statement explaining the reasons for the FSCA, including description of the device deficiency or malfunction, clarification of the potential hazard associated with the continued use of the device and the associated risk to the patient, user or other person and any possible risks to patients associated with previous use of affected devices.
4	Advice on actions to be taken by the user. Include as appropriate:
	identifying and quarantining the device,
	method of recovery, disposal or modification of device,
	recommended review of patients previous results or patient follow up, e.g., implants, IVD,
	timelines.
5	A request to pass the field safety notice to all those who need to be aware of it within the organization and to maintain awareness over an appropriate defined period.
6	If relevant, a request for the details of any affected devices that have been transferred to other organizations, to be given to the manufacturer and for a copy of the field safety notice to be passed on to the organization to which the device has been transferred.
7	If relevant, a request that the recipient of the field safety notice alerts other organizations to which incorrect test results from the use of the devices have been sent, for example failure of diagnostic tests.
8	Confirmation that the relevant national Competent Authorities have been advised of the FSCA.
9	Any comments and descriptions that attempt to play down the level of risk in an inappropriate manner or advertise products or services should be omitted.
10	Contact point for customers how and when to reach the designated person. An acknowledgment form for the receiver might also be included (especially useful for manufacturer's control purposes).

Guidelines on a Medical Devices Vigilance System (2013)

FSCA field safety corrective actions

gas analysis, and consumables and reagents for infection testing) were also excluded as they are typically used in laboratories (IVD for blood gas analyzes, IVD for infection testing) and intensive care units (IVD for blood gas analyzes), and in part were subject of prior studies (IVD for infection testing) (Hannig and Siekmeier 2015; Siekmeier et al. 2010). FSN of the included FSCA were analyzed in respect to the criteria of MEDDEV 2.12-1 rev 8 (Table 1). Research was carried out separately for FSN in German and English language, and for different product groups.

3 Results

3.1 Number of Reports and FSCA

Between January 1, 2000 and December 31, 2013 BfArM received a total of 61,904 reports regarding medical devices. Of these 57,356, 28,715, 28,641, and 4,548 reports were related to medical devices in total (both, active and non-active), active medical devices, non-active medical devices, and IVD, respectively. Out of the 61,904 reports, 50,053 were received within the study period of January 1, 2005 and December 31, 2013, from which 45,938, 23,394, 22,544, and 4,115 were related to medical devices in total (both, active and non-active), active medical devices, non-active medical devices, and IVD, respectively. Comparison of the notifications reported to the BfArM in the years 2000, 2005, and 2013 underlines a strong increment of reports to this Competent Authority (3,387 in 2005 *vs*. 1,934 in 2000: +75.1 %, 8,252 in 2013 *vs*. 1,934 in 2000: +326.7 %, and 8,252 in 2013 *vs*. 3,387 in 2005: +143.6 %). A total of 6,465 FSCA were publicized since January 1, 2005 of which 4,912 were related to active and non-active medical devices and 1,553 to IVD, which also

demonstrates a strong increase (1,077 in 2013 *vs.* 483 in 2005: +123.0 %) within the observation period (Table 2). Based on the inclusion criteria, only FSCA related to medical devices for use in pulmonology were analyzed in the present study. These were 41 FSCA mostly for active medical devices (6 nebulizers, 7 oxygen concentrators, 15 pulse oximeters, 4 lung function analyzers, and 9 devices serving for pleural drainage, treatment of lung emphysema, or bronchial stenosis).

3.2 Fulfillment of MEDDEV Criteria

German and English FSN were found in 36 and 35 cases, respectively (nebulizers 6/4, oxygen concentrators 5/6, pulse oximeters 15/13, lung function analyzers 2/3, and devices for pulmonary treatment 8/9) (Table 3). FSN were clearly characterized as such in 22/20 cases and names of the affected products were provided in 36/35 cases. Lot numbers were provided in 7/8 cases and other attributions for product identification was available in 26/24 cases, respectively. Detailed information regarding the FSCA and product malfunction was found in 27/33 and 36/35 cases, respectively. Product malfunction was due most frequently to a fault in construction and production of the product or an issue with the raw material and components of the product in 27/27 cases. Examples of these were issues in the power supply (mains adapter or battery, 5/5 cases), issues with overheating resulting in an increased fire hazard (5/5), and issues of sensor components (4/4 cases), likely as these components seem to be a fragile and sensitive part of the affected systems. In 3/2 cases a product deficiency could be excluded and the FSCA was made due to a revision of the standard specifications, preventive revision of instructions for use to implement further safety recognitions and preventive expansion of warning notices and protective measures in the instructions for use and in 1/1 case the manufacturer informed customers about product counterfeiting. A software error or an erroneous installation of software was reported in 2/2 cases and an invalid alerting was also reported in 2/2 cases of German and English FSN, respectively. In 1/1 case, a specific description of the product malfunction was impossible because the root-cause analysis was not finished at the time of the FSN.

Information on product related risks with previous use of affected medical devices was provided in 24/23 German and English FSN (Table 3). In most cases (12/12) products bear a direct risk for patients or users, e.g., shortcut or burning. In 4/4 cases the manufacturers informed affected customers about a risk of misdiagnosis, false therapeutic decisions or a delay in therapy. In 5/4 cases, the manufacturers informed about the presence of a potential risk but gave no specified information about the risk and in 2/3 cases a potential hazard could be excluded. A complete failure of the device was described in 1/0 (no English FSN available) case.

In 34/34 German and English FSN manufacturers provided information to mitigate product related risks (Table 3). These were instructions for risk mitigation, e.g., requirement of additional handling (5/3), additional safety instructions (2/3), stop of use and recall (24/25), and product destruction (2/1). In (1/2) cases no additional steps were required and the continued use was possible without any restrictions.

Requests to pass the FSN to persons or organizations needing awareness were found in 10/14 German and English FSN, respectively. Comments or descriptions understating the level of risk, e.g., “You, your customers, and particularly the patients using our products are very important and we know to appreciate your support in this matter”, or “Please be assured that the manufacturer is committed to consistently providing high quality products and services to our customers”, or “Please be assured that maintaining a high level of safety and quality is our highest priority” were found in (7/8) FSN. However, direct advertising, e.g., demonstration of new products and articles was never found in this study. Contact data were provided in 30/30 cases. Finally, confirmation that the Competent Authority was informed was found in 12/14 cases and in 19/18 cases a customer confirmation form was included (Table 3).

Table 2 Number of notifications to the BfArM 2000–2013 and number of FSCA publicized by the BfArM 2005–2013

	Active medical devices, except IVD	Non-active medical devices, except IVD	All medical devices, except IVD	IVD	Total
Year	Notifications	Notifications	Notifications (FSCA)	Notifications (FSCA)	Notifications (FSCA)
2000	926	987	1,913 (----)	21 (----)	1,934 (----)
2001	906	1,080	1,986 (----)	33 (----)	2,019 (----)
2002	995	1,213	2,208 (----)	58 (----)	2,266 (----)
2003	1,116	1,298	2,414 (----)	121 (----)	2,535 (----)
2004	1,378	1,519	2,897 (----)	200 (----)	3,097 (----)
2005	1,515	1,665	3,180 (348)	207 (135)	3,387 (483)
2006	1,769	1,858	3,627 (391)	235 (116)	3,862 (507)
2007	2,179	1,884	4,063 (388)	583 (150)	4,646 (538)
2008	2,290	2,087	4,377 (533)	506 (143)	4,883 (676)
2009	2,361	2,141	4,502 (615)	392 (149)	4,894 (764)
2010	2,792	2,506	5,298 (544)	482 (180)	5,780 (724)
2011	3,269	2,395	5,664 (666)	474 (194)	6,138 (860)
2012	3,400	4,238	7,638 (646)	573 (190)	8,211 (836)
2013	3,819	3,770	7,589 (781)	663 (296)	8,252 (1077)
All	28,715 from these 23,394 since begin 2005	28,641 from these 22,544 since begin 2005	57,356 from these 45,938 since begin 2005 (4,912 FSCA since begin 2005)	4,548 from these 4,115 since begin 2005 (1,533 FSCA since begin 2005)	61,904 from these 50,053 since begin 2005 (6,465 FSCA since begin 2005)

Siekmeier and Lütz (2007b), Siekmeier et al. (2008, 2009), Siekmeier and Wetzel (2013b), BfArM homepage (2014)

FSCA field safety corrective actions

Table 3 Compliance of the FSN to the criteria of Guideline MEDDEV 2.12-1 rev 8

	German/English
Number of FSCA	41
Number of FSN	36/35
FSN is clearly to identify as FSN for users	22/20
Declaration of the product name in the FSN	36/35
Declaration of the type of action	27/26
Declaration of the Lot-No.	7/8
Other attributes for product identification	26/24
Information regarding the reason of the FSCA	27/33
Description of the device malfunction in the FSN	36/35
Clarification of the potential hazard associated to continued use	24/23
Directions for mitigation of product related risk	34/34
Request to pass the FSN to other persons who need to be aware	10/14
Comments to play down the situation	7/8
Declaration of a contact person or phone number	30/30
Confirmation that the relevant national CA has been informed	12/14
Acknowledgement form for the receiver included in the FSN	19/18

Guidelines on a Medical Devices Vigilance System (2013)

FSCA field safety corrective actions, *FSN* field safety notices, *CA* Competent Authority

In a few cases, comparison of German and English FSN demonstrated differences in the number of complying MEDDEV criteria, differences of the FSN for the affected products (product or lot numbers), contact data of the manufacturers, and names of the informed Competent Authorities. In contrast, comparison of German and English FSN for potential differences of the measures to be taken by the users (e.g., due to differences in customer education) revealed no relevant deviations.

4 Discussion

Beside other regulations in cases of FSCA due to product failure, the guideline MEDDEV 2.12-1 rev 8 (Guidelines on a Medical Devices Vigilance System 2013) regulates the requirement of FSN publicized by the manufacturers in cases of FSCA. However, irrespective to the importance of FSN the number of publications investigating their quality is sparse (Hannig and Siekmeier 2015; Siekmeier et al. 2010). Here we studied the quality of FSN of medical devices serving for diagnostics or treatment in pulmonology in respect to the criteria of MEDDEV 2.12-1 rev 8. Since 2005, an increasing number of European Competent Authorities publicize information on FSCA on their individual homepages. Usually, Competent Authorities only provide information regarding FSCA affecting the country for which the Competent Authority takes responsibility and publication policy is also very different between distinct Competent Authorities. In consequence, numbers of publicized FSCA and affected products differ strongly between distinct European Competent Authorities. Our search on homepages of European Competent Authorities demonstrated that the very highest number of FSCA is publicized on the homepage of the German Competent Authority BfArM reflecting the size of the German market for medical devices and IVD, as well as the publication policy of this Competent Authority. Therefore, we analyzed only data publicized on the BfArM homepage (2014).

Between January 1, 2000 and December 31, 2013 BfArM received a total of 61,904 notifications from which 50,053 were received since January 1, 2005 demonstrating a strong increment of notifications (2005 *vs.* 2000: +75.1 %, 2013 *vs.* 2000: +326.7 %, and 2013

vs. 2005: +143.6 %). The corresponding numbers of FSCA showed also a strong increase (2013 *vs*. 2005: +123.0 %). The increments suggest a good function of the European system for market surveillance. In principle, these data are in accord with the results publicized by Henneghan et al. (2011) also reporting a strong increase of FSCA in the United Kingdom by 1,220 % within their observation period from 62 in 2006 to 757 in 2010. However, the strong increment reported in that study is influenced by a low number of FSCA reported in 2006 and the number of additional medical-device alerts publicized by the Medicines and Healthcare Products Regulatory Agency (MHRA) not included in this number which showed only a minor increase within the observation period (from 73 in 2006 to 100 in 2010, +37.0 %).

The ongoing increase of notifications may reflect both increasing acceptance of the European system (firstly established in 1994 for medical devices and 1998 for IVD) (Council Directive 93/42/EEC of 14 June 1993 concerning medical devices; Directive 98/79/EC of the European Parliament 1998) and underreporting in the past. Between January 1, 2005 and December 31, 2013 50,053 notifications were received by the BfArM of which 45,938 were related to medical devices (active and non-active) and 4,115 to IVD (except IVD in the responsibility of the Paul-Ehrlich-Institute) resembling 91.8 % and 8.2 % of the notifications related to these product groups, respectively. The corresponding numbers of publicized FSCA were 6,465, 4,912, and 1,553 for all products, active and non-active medical devices and IVD, resembling the corresponding proportions of 76.0 % and 24.0 %, respectively. The obvious differences in the proportions of notifications and FSCA between medical devices and IVD indicate differences between these types of products, e.g., in respect to their clinical use (e.g., patient treatment, or diagnostics), product type (active or non-active medical device, and IVD) and potential risk (risk for direct harm for users and patients (mainly in medical devices), risk for indirect harm for patients due to delayed or incorrect results (mainly in IVD). Due to the strong heterogeneity of products there are also differences within the group of IVD (e.g., lay use *vs*. professional use, tests and reagents *vs*. analyzers, clinical indications (e.g., clinical chemistry, hematology, or microbiology)) as reported before (Siekmeier and Lütz 2007a, b; Siekmeier et al. 2008; Siekmeier and Wetzel 2013a, b) but also within the group of medical devices (e.g., active *vs*. non-active, implantable *vs*. non-implantable devices) and medical devices risk classes (I: low risk, II: medium risk, and III: high risk) according the European classification (Henneghan et al. 2011).

In our study we included 41 FSCA related to medical devices for use in pulmonology which were active medical devices for diagnostics (pulse oximeters and capnometers, including one case related to a consumable), devices for pulmonary function testing, devices for oxygen therapy (concentrators), nebulizers, and non-active medical devices (for emphysema treatment, bronchial dilation and pleural drainage) resembling only 0.8 % of all FSCA related to medical devices except IVD publicized by the BfArM 2005–2013. However, this number reflects a very specific group of devices. Inclusion of other medical devices (e.g., respirators) and IVD such as blood gas analyzers and their consumables would significantly increase the number of included cases, but also cause a strong bias of the results due to large differences of these product groups.

German and English FSN were found in 36 and 35 out of 41 FSCA, respectively. Most likely, the differences between the numbers of FSCA and FSN, and the numbers of German and English FSN are caused by a number of missing FSN in cases where no FSN has been sent to the BfArM (e.g., information of few customers by phone only). The very most FSN were clearly characterized as FSN (22/20) and specified a type of action (27/26; e.g., recall, corrective measurement, or security information) and included the names of the affected products according to requirements of the MEDDEV 2.12-1 rev 8. Lot numbers and other information for product identification were also provided by most FSN, but the number of FSN complying with the MEDDEV criteria was smaller even though distinct product identification is essential in cases of

FSCA. In the majority of FSN, manufacturers provided sufficient information regarding the FSCA in cases of product malfunction. However, a critical non-compliance to the requirements of MEDDEV 2.12-1 rev 8 was found regarding the clarification of the potential hazard associated to continued use of the affected product (24/23 out of 36/35 German and English FSN, i.e., lack in about one third of FSN). These data are in accordance with the results of a previous study in IVD for infection testing (116/116 out of 157/154 German and English FSN (Hannig and Siekmeier 2015)). Such noticeable deviation from the requirements of the MEDDEV should be avoided as clear descriptions in these points serve as the basis for understanding the FSCA and required measures to be performed by the users for risk reduction. Information to mitigate product related risks was found in 34 out of 36 German and 34 out of 35 English FSN. Although these numbers are high one should consider that this information is essential in FSN in cases of product failure. No FSN included a recommendation of the manufacturer for control of the results or retesting. This observation stands in contrast to our previous publication for IVD for use in infection diagnostics where the recommendation for control of the results or retesting was frequently found (69/75 out of 157/154 German and English FSN) (Hannig and Siekmeier 2015). This difference can be explained by different types of included products in both studies. In the present study only 19 out of 41 medical devices (15 pulse oximeters and capnometers and 4 lung function analyzers) served for diagnostic purposes, whereas the remaining medical devices served for patient treatment and therefore control of results or retesting played no role. In contrast, IVD serve exclusively for diagnostics and recommendation of control of results or retesting serves for correction of obtained erroneous results due to product failure. Furthermore, it is likely that product failure in medical devices for use in pulmonology (e.g., obvious lack of function or obviously implausible results in pulse oximeters and lung function analyzers) are more easily detectable than plausible but incorrect results in IVD tests. Requests to pass the FSN to persons or organizations needing awareness were found in 10/14 FSN only. However, these requests are necessary to ensure the spread of the information because different users and split responsibilities may exist within organizations. Contact data were also provided in 30/30 FSN, which may also be critical as users may have queries regarding the FSCA. Although comments which attenuate the situation were found only in a minor number of FSN (7/8), this is of importance because FSN are issued in cases of product failure and product related risk and these comments foil the intention of the FSN. Customer confirmation forms were included in the majority of FSN (19/18). However, they should be included in the FSN as they are useful for manufacturer's control purposes.

In principle, failures of medical devices and IVD can cause two types of harm for patients, users, or third persons. These are direct harm, e.g., due to burn, electrical hazard, bleeding and infection, and indirect harm due to erroneous or delayed results of analyzes (Siekmeier and Lütz 2007a, b; Siekmeier et al. 2008, 2009). Depending on the type of product, medical devices for use in pulmonology bear the risk of both direct and indirect harm. For example, direct harm can be caused by electrical failure of pulse oximeters, failure of oxygen concentrators and nebulizers, and failure of devices for emphysema treatment, bronchial dilation and pleural drainage. On the other hand, indirect harm due to delayed or erroneous results of analyzes can be found in pulse oximeters, capnometers and devices for pulmonary function testing. Therefore, there is a need for product specific analyzes considering differences between the distinct medical devices.

In our present study we observed a very homogenous picture with no obvious deviations between the different subgroups of the included medical devices. The very most cases of product failures were due to design or manufacturing deficiencies, e.g., fault in construction or product production or an issue with raw material or components of the product (27 out of 36 German and 27 out of 35 English FSN). In principle, this confirms prior results publicized by Davis et al. (2011) analyzing FSN relating to medical device recalls 2005–2009 publicized on the

European Commission (EC) national Competent Authority report database who observed that another group of issues related to medical devices, cardiovascular recalls are almost exclusively design or manufacturing issues, while other therapeutic areas have more diverse reasons for a recall. It also confirms the results reported by the Battelle Memorial Institute which reviewed FDA high-priority Class I recalls from January 2005 to May 2010 and reported that approximately 50 % of the recall causes of devices in the review period were attributed to design deficiencies (flaw inherent in the design of the device, either created initially or through approved design changes), 29 % to manufacturing deficiencies (failure to maintain sterility, failure to follow Good Manufacturing Practices or manufacturing quality control (QC) deficiencies), and 6 % to labeling deficiencies (Battelle Memorial Institute 2010). It should be considered that this study analyzed Class I recalls (high risk) according to FDA classification representing only a subset of all recalls which may differ from Class II (moderate risk) and Class III (low risk) recalls (Battelle Memorial Institute 2010; Davis et al. 2011; Henneghan et al. 2011), whereas our study did not discriminate FSCA in respect to the underlying risk. Moreover, authors of the Battelle Memorial Institute did not differentiate between the distinct types of medical devices including IVD and it is likely that there are relevant differences. For example, analyzing IVD for diagnostics of infectious diseases (mostly tests and reagents and a few analyzers based on cultural means) in a prior study we observed a very heterogeneous spectrum of product failures described in the FSN released by the manufacturers (Hannig and Siekmeier 2015). In detail in these IVD manufacturing issues and raw material failure were also an important source of malfunction (27 out of 147 cases), but many other examples of product deficiencies, e.g., microbiological contamination of the product, packaging issues or failure in the package insert were also found.

In the present study performed in medical devices for use in pulmonology we observed a high direct risk of hazard for patients and users provoked, e.g., due to fire hazard or shortcut reported in 12 German and English FSN (out of 41 included cases). This proportion is much higher than in IVD analyzed in our prior study (risk of poisoning, contamination, stick injury, or infection reported in 4 out of 157 German and 4 out of 157 English FSN) (Hannig and Siekmeier 2015). Most likely, this deviation is caused by the high number of active (electrical) medical devices included in the present study when compared to the prior study in IVD including mostly tests and reagents. However, the high risk for fire hazard and short cut in active medical devices for use in pulmonology indicates the need for further improvements in design and development of these products to enhance product safety and to minimize the risk for patients and users.

Comparison of German and English FSN not only demonstrated differences in the number of complying MEDDEV criteria but also differences in the affected products (product or Lot-No.), contact data of the manufacturer and the name of the informed Competent Authority. These differences are most likely caused by distribution of divergent products or lots, different national subsidiaries of the manufacturers and different responsible Competent Authorities within different countries and assumed to be not critical. However, there were also cases of differences of requests for passing the FSN to other persons and organizations (e.g., due to different types of laboratory or hospital organization within different countries) which may be critical and therefore should be subject of thorough evaluation.

In summary, the data show a strong increase of notifications to the BfArM and also the number of FSCA in all groups of medical devices (active medical devices, non-active medical devices, and IVD). The high numbers of notifications to the BfArM and FSCA publisized by the BfArM demonstrate that the European surveillance system for medical devices and IVD is an established tool for ensuring the safety of medical devices. However, there is a need for some further optimization. For example, as the distribution of FSN in cases of FSCA is an important mean to reduce product related risks of medical devices already in the market, the type and content of publicized FSN should comply with the requirements of the Guideline MEDDEV 2.12-1 rev 8.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Unmet Needs of Patients with Chronic Respiratory Diseases Within Primary Healthcare

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Abstract

There is no data on the level of unmet needs in the heterogenic group of chronically ill patients. The purpose of this study was to define the degree of unmet needs in patients with chronic respiratory diseases and to identify the factors that determine them. The study group consisted of 214 adult patients with the median age of 65 (min–max: 18–90 years). Variables affecting the level of satisfied needs were the following: gender, age, marital status, place of residence, number of chronic diseases, somatic symptoms, level of disease acceptance, level of quality of life (QoL), and health behaviors. The prevention program to increase the level of satisfied needs in patients with chronic respiratory diseases, apart from obviously being addressed to those with low levels of health satisfaction and quality of life indices, should be addressed to men, the elderly, those having no partner, living in the countryside, and having multiple somatic symptoms. Patients with a high level of disease acceptance, those maintaining physical quality of life and advantageous health behaviors should be considered as well.

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Keywords
Coordination of care • Bio-psycho-social model • Chronic Care Model • Family medicine • Family physicians

1 Introduction

The number of people with disabilities due to chronic diseases in the world is constantly growing due to an aging population, an increased risk of disability in the elderly and a global increasing frequency of chronic diseases that cause disability (diabetes, cardiovascular diseases, and mental illnesses). It is estimated that countries with low and middle income chronic diseases are responsible for 66.5 % of all years lived with disability (WHO 2008). Patients with chronic health impairment more frequently experience inconvenience and report unmet health needs, particularly in the area of information (Schoen et al. 2014). Also, patients with chronic diseases and are in poor or very poor condition, most often report unsatisfied needs (Allin and Masseria 2011).

However, health needs of the chronically ill are rarely driven in analyzes of primary healthcare. It is proposed that they are the result of the level of clinical status, quality of life, disease acceptance, health behaviors, and the quality of health services. In the process of developing primary healthcare in accordance with the principles of the Chronic Care Model, there is a need to estimate individual biopsychosocial needs of patients, which may help determine the clinical management and patient care (Schoen et al. 2014). It is assumed that the recognition of needs (especially unsatisfied needs) is equivalent to the identification of the problem and enables appropriate intervention (Orrell and Hancock 2004). It is also underlined that the identification of needs, especially the unsatisfied ones, is important because of their relationship with the status of health, quality of life and medical costs (Walters et al. 2000). Most importantly, one of the methods to measure equal access to health care for the chronically ill is the assessment of the reports of unmet health needs of any reason (OECD 2012).

It is noted that the needs assessment is a stronger explanatory variable with impact on life quality than clinical or sociodemographic factors, as well as it is indirectly associated with the level of provided care (Schoen et al. 2014). In addition, it has been found that in the comparison of the needs assessment done by patients and health care professionals – the assessment of the patients are more accurate (Slade et al. 1998) and the extent to which needs are unsatisfied corresponds to the level of functioning of patients (Schoen et al. 2014).

Therefore, determining the level of needs complements the estimation of current patient interaction with the healthcare system. Proper evaluation of patients' needs within the Chronic Care Model informs about the current functioning of patients.

Prevalence of unmet needs vary from 2.6 to 34.6 % among those over 65 years old with a disability (Newcomer et al. 2005). In Europe it has been found (self-reported unmet need and forgone care) that the unsatisfied needs of Europeans aged 50 years and more are the result of lack of care, poor access to healthcare services, and the high costs of healthcare. Barriers to access health services are complex, usually are a consequence of the health status, as well as the health care itself and of social and cultural context (OECD 2012). Groups that report most often unmet health needs, mainly due to difficulties in access to healthcare, are women and people with low income. In Greece, Italy, Poland, and Portugal, this applies to 5 % of patients with the lowest incomes – the most common causes are the following: the cost of treatment, waiting time for health services, and distance from health care facilities (OECD 2012).

According to the representative of the Polish population survey results – more than 1.8 million people in Poland have difficulties with

maintaining daily hygiene and more than 1.6 million people with dressing themselves. Close to 2.2 million adults report difficulties associated with laying down and getting up from bed or sitting down or standing up from a chair. Nearly 890,000 adults have difficulties in using the toilet, and more than 475,000 present problems with eating. One in six adult Poles has difficulty performing heavy housework, 1.3 million people have difficulty in meals preparation, 900,000 have problems with using the phone, 2.5 million people with daily shopping, and 660,000 with preparation and drugs intake. Nearly 40 % of 70 year old adults and older people report difficulties with basic self-service, every second person above 70 did not receive any help, and 20 % of adults – would like to get help or to improve previous help (CBOS 2010).

The analysis of the degree of patients' needs satisfaction in primary care is the key to the observed increase in prevalence of biopsychosocial dysfunctions in chronically ill patients. At the same time, there is not enough data about the level of met/unmet needs in heterogenic group of chronically ill – the most common group of patients in primary healthcare.

Considering the above outlined, the purpose of this study was to determine the degree of satisfied and unsatisfied needs of patients with chronic respiratory diseases and to identify the factors that identify them in this group of patients.

2 Methods

The research was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Bioethical Commission of the Medical University in Wrocław (approval no. KB-608/2011). The main inclusion criteria were: age (at least 18 years old) and the diagnosis of at least one respiratory chronic disease.

The study group consisted of 214 adult patients with chronic respiratory diseases. The median age 65 years (min–max: 18–90 years). Participants for the study were recruited from patients of 130 general practitioners between July 2011 and April 2013. The project staff members asked eligible patients if they would like to take part in the study. The patients who agreed to participate anonymously in the project signed an informed consent form. The patients were given a questionnaire to complete at home and return in a stamped envelope.

A level of met/unmet needs was assessed with the Modified Short Camberwell Needs Assessment. The questionnaire focuses on 22 problem areas for patients with chronic somatic diseases (without severe mental disorders). In order to standardize the results obtained the following coding was established: 0 denoting the state of unmet needs and 1 denoting the state of satisfied needs. On the basis of 24 questions characterizing 22 needs, a number of needs was set for the patient to answer whether the need was met (1) or not (0). Then, among needs (N), the number of satisfied needs (M) was established. Camberwell index was calculated according to the formula: M/N. Internal consistency of the Modified Short Camberwell Needs Assessment was Cronbach's alpha = 0.96.

Quality of life was assessed with the Polish version of the World Health Organization Quality of Life Instrument Short Form (WHOQOL-BREF) (Wolowicka and Jaracz 2001; WHOQOL Group 1998). The WHO Quality of Life (WHOQOL) is a generic quality of life instrument that has been designed to be applicable to people living in different conditions or cultures (Jaracz et al. 2006). The WHOQOL-BREF can be used to measure quality of life within four domains: D1 – Physical, D2 – Psychological, D3 – Social relationships, and D4 – Environmental. Answers to all the questions of the WHOQOL-BREF are on a five point Likert-type scale including the first two questions about satisfaction with QoL and health state. The reliability of the Polish version of the WHOQOL-BREF questionnaire, measured with the α-Cronbach coefficient refers both to the parts evaluating particular domains (results from 0.81 to 0.69) and the questionnaire as a whole (0.90) (Jaracz et al. 2006; Bousquet et al. 1994).

The patients' adaptation to a lifestyle with a disease was assessed using the Acceptance of Illness Scale (AIS) developed by Felton et al. (1984), and adapted to Polish conditions by Juczynski (2009). The AIS consists of eight statements about negative consequences of health state, where every statement is rated on a five-point Likert-type scale. Number 1 denotes poor adaptation to a disease, and 5 its full acceptance. The score for illness acceptance is a sum of all points and can range from 8 to 40. Low scores (0–29) indicate the lack of acceptance and adaptation to a disease and the strong feeling of mental discomfort. High scores (35–40) indicate the acceptance of illness, manifested as the lack of negative emotions associated with a disease. The scale can be used to assess the degree of acceptance of every disease. The α-Cronbach coefficient of the Polish version is 0.85 and that of the original version is 0.82 (Juczynski 2009; Felton et al. 1984).

We also used the Health Behavior Inventory (HBI) developed by Juczynski (2009). The instrument consists of 24 statements that measure four categories of pro-health behavior: healthy eating habit; preventive behavior; positive mental attitudes; and health practices. The patients mark the frequency related to health behavior and the right activity connected with health: 1– almost never, 2 – rarely, 3 – from time to time, 4 – often, 5 – almost always. The sum of the results from all four scales indicates the score for general health behavior (range 24–120), where the score correlated with the intensity of healthy behavior (the higher the score, the more healthy behavior). The intensity of health behavior in particular categories is the sum of all answers on a particular sub-scale divided by six. The HBI internal consistency measured with α-Cronbach equals to 0.85 (Juczynski 2009).

The somatic index was calculated for each patient. Somatic symptoms reported by the patients were assigned the values from one (symptoms occurring once a year) to seven (permanent symptoms). The index was calculated by summing up values assigned to somatic symptoms, and then dividing this sum by 49 (the highest possible score for the frequency of somatic symptoms).

The index of services was calculated by summing up the received services, and dividing the obtained sum by the number of types of the received services provided during visits to a doctor during the last 12 months.

2.1 Statistical Elaboration

The Shapiro-Wilk test was employed to verify normality of distributions of variables. Arithmetic means, standard deviations, medians, as well as the range of variability (extremes) were calculated for measurable (quantitative) variables; while for qualitative variables, the frequency (percentage) was determined. The analysis of qualitative variables was based on contingency tables and the chi-square test or Fisher's exact test for count data. The Spearman rank correlation test was used to check correlations between the variables. Overall results, except for the level of healthy eating habits, were not normally distributed.

Analysis of logistic regression was used in order to examine the impact of explanatory variables on the response variable. The logistic regression was performed using a method of an in-depth analysis of all models with a number of 19 to 6 explanatory variables selected from the set of 19 variables. Explanatory variables were always selected from the group of those 19 variables: sex, having a partner, place of residence, level of illness acceptance, satisfaction with QoL, satisfaction with quality of health state, level of QoL in Physical Domain, level of QoL in Psychological Domain, level of QoL in Social relationship Domain, level of QoL in Environmental Domain, level of healthy eating habits, level of preventive behaviors, level of positive mental attitudes, level of health practices, age, BMI, level of satisfaction from health care, somatic index and number of chronic diseases.

The study began with a full model that includes the variable Camberwell and 19 explanatory variables with no intercept. Next, the number of explanatory variables was reduced. The first significant models began to appear in the 7 explanatory variables in the model. Smaller

models have not been studied. The entire procedure was repeated for models with intercept. The first important models began to appear in the 6 explanatory variables in the model (13 models). Smaller models have not been studied. For further analysis 4 models of 7 explanatory variables, without the intercept, were selected.

The analysis of the logistic regression was used in order to examine the impact of explanatory variables on the odds ratio (OR) of Camberwell index. The chance was defined as the ratio of probability of a certain event to the probability of the opposite event. The chance quotient was defined as the ratio of probability that a certain event happens in one group to the probability that it happens in the other group.

Correspondence analysis was used to provide information similar to the interpretation of the results of the factor analysis, but on qualitative variables. This method allows intuitive inference about relationships occurring between categories of variables. With the help of the correspondence analysis the following profiles were determined: subjects with lower Camberwell index and subjects with higher Camberwell index. Each variable used in the analysis of correspondence was first converted to bicategorial feature to ensure the best interpretation of clusters in a two-dimensional graph. As a result of the correspondence analysis carried out for a set of bicategorial variables a two-dimensional graph is obtained, which is a set of 2n points. Each point corresponds to one category. The set of points forms a cluster, i.e., subset of points located close to each other. Correspondence analysis method lies in the fact that the categories (points) belonging to clusters are interpreted as related to each other. The critical level of significance was assumed at $p < 0.05$. The R 3.0.2 (for Mac OS X 10.9.4) statistical software was used for all data analyses.

3 Results

Majority of patients were women (113, 53.1 %), at age 65 and over (108, 51.2 %) and from urban areas (137, 64.9 %). Detailed socio-demographic data of the patients and their chronic diseases are shown in Table 1. The median number of chronic diseases was 3 (min–max: 1–15), BMI (body mass index): 27.9 (min–max: 18.6–41.0) kg/m^2, while the somatic index: 0.4 (min–max: 0.0–1.0). The median Camberwell index was 0.8 (min–max: 0.2–1.0). The results obtained from the 22 fields of met/unmet needs are shown in Table 2. The median of disease acceptance level was low (27 points, min–max: 8–40). The median of satisfaction with the quality of life was 4 (min–max: 1–5), while with the health state: 3 (min–max: 1–5). The highest median among the quality of life domains was found in the field of social relationship (14.7, min–max: 5.3–20.0), lower in the environmental domain (13.5, min–max: 8.5–19.5), and the lowest in the psychological (13.3, min–max: 5.3–19.3) and physical (13.1, min–max: 4.0–19.4) domains.

Within the pro-health behaviors, the highest median was found in the category of preventive behaviors (3.8, min–max: 1–5), lower in the category of positive mental attitudes (3.7, min–max: 1.5–5.0), and the lowest in the categories of health practices (3.6, min–max: 1.5–5.0) and healthy eating habits (3.3, min–max: 1.0–5.0).

3.1 Results of Correlations

A low Camberwell index was more frequently reported by seniors ($r = -0.28$, $p = 0.0004$) with no relationship ($r = 0.24$, $p = 0.0003$), with the low level of acceptance of the disease ($r = 0.40$, $p = 0.0001$), low level of satisfaction with QoL ($r = 0.48$, $p = 0.0001$), low level of satisfaction with the quality of health state ($r = 0.42$, $p < 0.0001$), low level of QoL in the physical domain ($r = 0.55$, $p < 0.0001$), low level of QoL in the psychological domain ($r = 0.68$, $p < 0.0001$), low level of QoL in the social relationship domain ($r = 0.62$, $p < 0.0001$), low level of QoL in the environmental domain ($r = 0.57$, $p < 0.0001$), low level of healthy eating habits ($r = 0.30$, $p < 0.0001$), low level of preventive behavior ($r = 0.20$, $p = 0.0038$), low level of positive mental

Table 1 Sociodemographic data and diagnoses (according to the ICD-10) of patients

	n = 214	n	%
Gender	Women	113	53.1
	Men	100	46.9
Age (year)	24 and below	6	2.8
	25–44	25	11.8
	45–64	72	34.1
	65–84	97	46.0
	85 and above	11	5.2
Place of residence	Village	74	35.1
	City/town population:		
	Below 5,000	28	13.3
	5,000–10,000	14	6.6
	10,000–50,000	50	23.7
	50,000–100,000	18	8.5
	100,000–200,000	17	8.1
	Over 200,000	10	4.7
Education	Primary	40	19.0
	Vocational	62	29.5
	Secondary	59	28.1
	Post-secondary	25	11.9
	Higher	24	11.4
Marital status	Single	28	13.2
	Married	121	57.1
	Divorced	9	4.2
	Widowed	54	25.5
Diagnosis	J44 Other chronic obstructive pulmonary diseases	80	37.4
	J45 Bronchial asthma	78	36.5
	J43 Pulmonary emphysema	32	15.0
	J42 Unspecified chronic bronchitis	27	12.6
	J41 Chronic simple and mucous- purulent bronchitis	25	11.7
	J47 Bronchiectasis	8	3.7
Most common co-existing diseases[a]	I10 Primary hypertension	92	43.0
	M47 Spondylosis	63	29.4
	I70 Atherosclerosis	39	18.2
	M15 Osteoarthritis of multiple joints	22	10.3
	I25 Chronic ischemic heart disease	21	9.8

[a]Some patients were diagnosed as having at least two pathological entities

attitudes ($r = 0.35$, $p < 0.0001$), low level of satisfaction from health care ($r = 0.19$, $p = 0.0298$), high somatic index ($r = -0.24$, $p = 0.0004$), high index of services ($r = -0.22$, $p = 0.0014$), and a high number of chronic diseases ($r = -0.40$, $p < 0.0001$). There was no statistically significant correlation between the results of Camberwell index and gender, place of residence, level of health practices, BMI, and the hospitalization index.

Men more frequently remained in stable relationships ($r = 0.18$, $p = 0.0018$). In addition, the following was observed in men: low level of healthy eating habits ($r = -0.25$, $p = 0.0003$), low level of preventive behavior ($r = -0.21$, $p = 0.0024$), and low level of positive mental attitudes ($r = -0.16$, $p = 0.0244$). In people without a permanent relationship, quite common was a low level of satisfaction with QoL ($r = 0.14$, $p = 0.0121$), low level of QoL in the social relationship domain ($r = 0.19$,

Table 2 Met/unmet needs of patients

No	Needs	n %	unmet	met	Total
1	Accommodation	n	15	188	203
		%	7.4	92.6	100
2	Food and grocery (shopping)	n	51	162	213
		%	23.9	76.1	100
3	Looking after the home	n	49	161	210
		%	23.3	76.7	100
4	Self-care at home	n	37	163	200
		%	18.5	81.5	100
5	Daytime activities	n	62	150	212
		%	29.3	70.8	100
6	Physical health	n	86	124	210
		%	41.0	59.1	100
7	Psychical health	n	43	110	153
		%	28.1	71.9	100
8	Information on condition and treatment	n	27	159	186
		%	14.5	85.5	100
9	Psychological distress	n	93	116	209
		%	44.5	55.5	100
10	Drinking alcohol and problems associated with drinking	n	15	89	104
		%	14.4	85.6	100
11	Narcotics	n	6	208	214
		%	2.8	97.2	100
12	Medicines that are not prescribed	n	148	63	211
		%	70.1	29.9	100
13	Social life	n	56	156	212
		%	26.4	73.6	100
14	Intimate relationships	n	18	43	61
		%	29.5	70.5	100
15	Satisfaction with intimate relationships	n	13	93	106
		%	12.3	87.7	100
16	Satisfaction with sexual life	n	73	101	174
		%	42.0	58.1	100
17	Need of having children	n	18	11	29
		%	62.1	37.9	100
18	Satisfaction with relationship with children	n	6	104	110
		%	5.5	94.6	100
19	Possibility of communication by phone	n	12	199	211
		%	5.7	94.3	100
20	Possibility of using public transport	n	47	85	132
		%	35.6	64.4	100
21	Ability of budgeting own money	n	20	189	209
		%	9.6	90.4	100
22	Getting all the money entitled to	n	58	85	143
		%	40.6	59.4	100

$p = 0.0007$), and a high number of chronic diseases ($r = -0.11$, $p = 0.0475$). For people living in rural areas, we found the following: advanced age ($r = 0.13$, $p = 0.0271$), low level of disease acceptance ($r = -0.21$, $p = 0.0005$), and low level of QoL in the psychological domain ($r = -0.21$, $p = 0.0002$).

3.2 Odds Ratio – Camberwell Index

The results of the logistic regression are shown in Tables 3 and 4. In women, the chance of a high Camberwell index is 2.1 times higher than in men, as well as in younger patients (chance 14 times higher), in the ones having a partner (2.2 times greater chance), and in those living in major cities (2.7 times greater chance of high Camberwell than in rural areas). A low number

Table 3 Results of logistic regression

i	Variables	Estimate β_i	Std. Error	z-value	Pr(>|z|)
Models with 7 variables					
Model 1 (n = 191)					
Chi^2 statistic of deviance = 55.47, df = 7, p <0.00001, pseudo R^2 = 0.21					
1	Gender	−0.757	0.344	−2.201	0.028
2	Having a partner	0.808	0.363	2.226	0.026
3	Places of residences	−0.124	0.061	−2.027	0.043
4	Level of illness acceptance	−0.053	0.026	−2.077	0.038
5	Satisfaction with quality of health state	0.508	0.213	2.386	0.017
6	QoL in Social Relationship Domain	0.248	0.065	3.795	0.001
7	Age	−0.036	0.009	−4.104	0.001
Model 2 (n = 170)					
Chi^2 statistic of deviance = 57.52, df = 7, p <0.00001, pseudo R^2 = 0.24					
1	Gender	−0.778	0.368	−2.113	0.035
2	Having a partner	0.816	0.391	2.086	0.037
3	QoL in Psychological Domain	0.284	0.067	4.263	0.001
4	Level of preventive behavior	0.795	0.337	2.360	0.018
5	Level of health practices	−0.988	0.374	−2.644	0.008
6	Age	−0.026	0.013	−2.084	0.037
7	Somatic index	−2.120	0.992	−2.137	0.033
Model 3 (n = 163)					
Chi^2 statistic of deviance = 50.79, df = 7, p <0.00001, pseudo R^2 = 0.22					
1	Places of residences	−0.177	0.072	−2.459	0.014
2	Level of illness acceptance	−0.066	0.029	−2.229	0.026
3	QoL in Environmental Domain	0.376	0.105	3.573	0.001
4	Level of positive mental attitudes	1.195	0.411	2.907	0.004
5	Level of health practices	−1.142	0.394	−2.900	0.004
6	Age	−0.028	0.013	−2.183	0.029
7	Somatic index	−2.036	0.974	−2.090	0.037
Model 4 (n = 173)					
Chi^2 statistic of deviance = 65.64, df = 7, p <0.00001, pseudo R^2 = 0.27					
1	QoL in Physical Domain	−0.219	0.097	−2.263	0.024
2	QoL in Psychological Domain	0.258	0.124	2.078	0.038
3	QoL in Social Relationship Domain	0.201	0.093	2.159	0.031
4	Level of positive mental attitudes	0.793	0.391	2.025	0.043
5	Level of health practices	−0.964	0.382	−2.526	0.012
6	Age	−0.027	0.013	−2.033	0.042
7	Number of chronic diseases	−0.280	0.010	−2.807	0.005

Response variable: Camberwell index

Estimate β_i – estimated coefficient β_i in the regression equation; Std. Error – estimated standard error of coefficient β_i; z-value – value of normal reference distribution; Pr(>|z|) – two-tailed p-value corresponding to the z-value

Table 4 Odds ratios from models of logistic regression for Camberwell index

	Per unit			Per range			
Variables	OR	95 % CI	1/OR	OR	95 % CI	1/OR	Range
Model 1							
Gender: Female (1), Male (2)	0.47	0.23–0.91	2.13	0.47	0.23–0.91	2.13	1
Having a partner: no (0), yes (1)	2.24	1.11–4.63	0.45	2.24	1.11–4.63	0.45	1
Place of residence (1–9)[a]	0.88	0.78–0.99	1.14	0.37	0.14–0.96	2.69	8
Level of illness acceptance: 8–40	0.95	0.90–0.99	1.05	0.18	0.03–0.87	5.50	32
Satisfaction with quality of health state: 1–5	1.66	1.10–2.55	0.60	7.64	1.48–42.53	0.13	4
QoL in Social Relationship Domain: 4–20	1.28	1.13–1.47	0.78	52.59	7.40–451.60	0.02	16
Age: 18–92	0.97	0.95–0.98	1.03	0.07	0.02–0.23	13.86	74
Model 2							
QoL in Psychological Domain: 4–20	1.33	1.17–1.52	0.75	93.80	12.68–845.60	0.01	16
Level of preventive behavior: 1–5	2.22	1.16–4.40	0.45	24.09	1.83–373.67	0.04	4
Level of health practices: 1–5	0.38	0.17–0.76	2.69	0.02	0.001–0.33	52.10	4
Somatic index: 0–1	0.12	0.02–0.81	8.33	0.12	0.02–0.81	8.33	1
Model 3							
QoL in Environmental Domain: 4–20	1.46	1.19–1.81	0.69	409.68	17.15–13074	0.002	16
Level of positive mental attitudes: 1–5	3.30	1.53–7.72	0.30	118.95	5.42–3548	0.008	4
Model 4							
QoL in Physical Domain: 4–20	0.80	0.66–0.97	1.25	0.03	0.001–0.57	33.43	16
Number of chronic diseases: 1–15	0.76	0.62–0.91	1.32	0.02	0.001–0.28	50.47	14

OR odds ratio, *CI* confidence interval

[a]Place of residence: city: (1) over 200,000; (2) 100,000–200,000; (3) 50,000–100,000; (4) 20,000–50,000; (5) 10,000–20,000; (6) 5,000–10,000; (7) 2,000–5,000; (8) below 2,000; (9) village

of chronic diseases (1) have approx. 50 times greater chance of a high Camberwell index compared with the high number of chronic diseases (15). The chance for a high Camberwell index in patients with somatic index equals to 0 is 8.3 times higher than in the group with index equal to 1. Among patients with a low level of disease acceptance there is a 5.5 times higher chance of the high Camberwell index, compared with the ones with a high level of acceptance. However, the high satisfaction with quality of health state has a 7.6-times greater chance of the high Camberwell index than in those with low levels of satisfaction. High levels of quality of life in the environmental domain mean approx. 410 times greater chance of the high Camberwell index when compared with low quality of life in that domain. Likewise, high level of quality of life in the psychological domain means approx. 94 times greater chance of the high Camberwell index when compared with low quality of life. A high level of quality of life in the social relationship domain represents a 52.6-fold bigger chance of the high Camberwell index. In contrast, low level of quality of life in the physical domain has about 33 times greater chance of the high Camberwell index when compared with a high level of quality of life in this area. High levels of positive mental attitudes mean approx. 119 times greater chance of the high Camberwell index (*vs*. low levels of these behaviors). A high level of preventive behaviors means 24 times greater chance of the high Camberwell index when compared with low levels of these behaviors. Finally, low levels of health practices mean 52 times bigger chance of the high Camberwell index when compared with a high level of the behavior.

3.3 Correspondence Analysis

Effects of the variables on the level of met/unmet needs are shown in Fig. 1. The graph shows that a

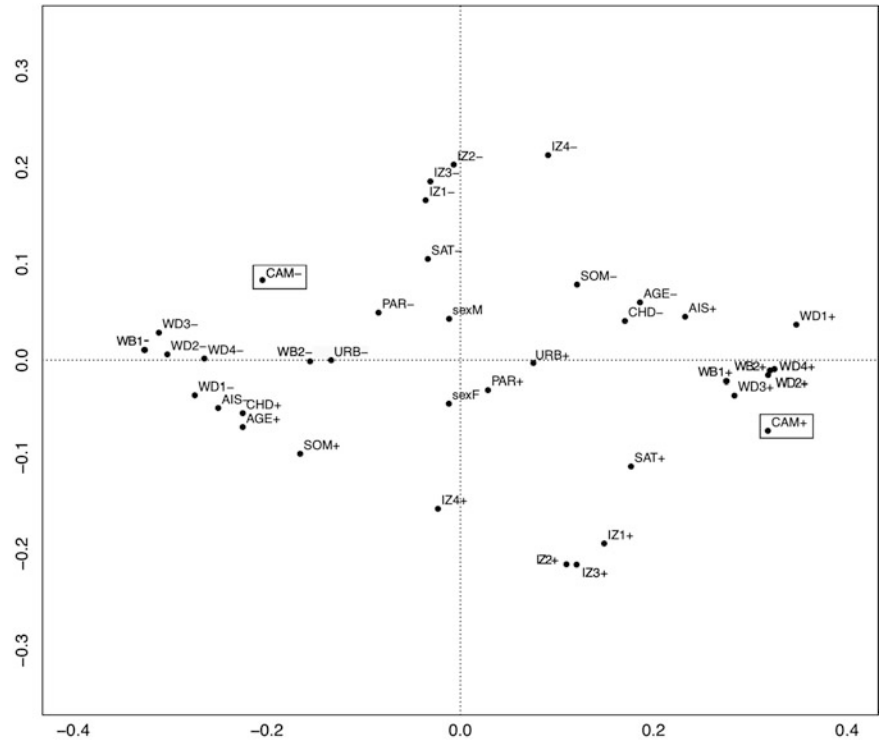

Fig. 1 Results of correspondence analysis – variable defined: Camberwell index (CAM). Legend: Sex (sexF: female, sexM: male); PAR – Having a partner (−PAR: no, +PAR: yes); URB – Place of residence (−URB: rustically area, +URB: urban area); AIS – Level of illness acceptance (−AIS: ≤median, +AIS: >median); WB1 – Satisfaction with QoL (−WB1: ≤median, +WB1: >median); WB2 – Satisfaction with quality of health state (−WB2: ≤median, +WB2: >median); WD1 – Level of QoL in Physical Domain (−WD1: ≤median, +WD1: >median); WD2 – Level of QoL in Psychological Domain (−WD2: ≤median, +WD2: >median); WD3 – Level of QoL in Social relationship Domain (−WD3: ≤median, +WD3: >median); WD4 – Level of QoL in Environmental Domain (−WD4: ≤median, +WD4: >median); IZ1 – Level of healthy eating habits (−IZ1: ≤median, +IZ1: >median); IZ2 – Level of preventive behaviors (−IZ2: ≤median, +IZ2: >median); IZ3 – Level of positive mental attitudes (−IZ3: ≤median, +IZ3: >median); IZ4 – Level of health practices (−IZ4: ≤median, +IZ4: >median); AGE – Age (−AGE: ≤median, +AGE: >median); SAT – Level of Satisfaction form health care (−SAT: ≤median, +SAT: >median); SOM – Somatic index (−SOM: ≤median, +SOM: >median); CHD – Number of chronic diseases (−CHD: ≤median, +CHD: >median); CAM – Camberwell index (−CAM: ≤median, +CAM: >median)

high level of satisfied needs most frequently co-occurs with high quality of life in all domains. In addition, a weaker relationship was observed between high level of acceptance of the disease, low number of chronic diseases, or younger age, and a high level of satisfaction with health care. A low level of satisfied needs frequently co-existed with low quality of life in all domains and with being a resident of rural areas as well as being single. A weaker relationship of a low level of satisfied needs was observed with a low level of disease acceptance, high number of chronic diseases, and older age. There were no links to the level of unmet/met needs demonstrated in the case of health practices level, having a partner, residing in urban area, low level of somatic index, and gender.

4 Discussion

In the group of patients with a chronic illness, most patients reported that they have good living conditions with access to a telephone, they cope well with the management of their money, they prepare meals, they can take care of the house,

and they have no difficulty in maintaining hygiene and are happy with how they spend a typical day. They are pleased with how they receive information on medicines and treatment, they do not abuse alcohol or take narcotics, and are satisfied with their social life. Regarding those without a partner, most would not want to change their marital status. Those in a relationship do not have problems with their partners. The majority of respondents had children and reported no problems related to taking care of them. Meanwhile, those with no children – more than half of them would like to have children. Most of the respondents confirmed that they feel good physically and mentally, they have no difficulties using public transportation, have a partner, are satisfied with their sex life, but only 6 of 10 patients confirmed a low level of stress. Only 3 out of 10 patients with chronic diseases admit to no medicine intake without recommendations from their physician – a phenomenon extremely dangerous from the point of the consequences of polypharmacy, including pharmacokinetic and pharmacodynamic interactions. These results correspond to the analysis of Ipsos (2010). The report determined that 70 % of Poles treat pain without medical consult. The most frequently used medicines were analgesics. According to a report conducted by CBOS (2010), 53 % of Poles using for the first time an over-the-counter medicine do not consult its use with their physician or pharmacist, and 13 % do not read the information leaflet.

Fourteen out of 100 patients in the study group reported that alcohol causes their health problems and endangers work and family relationships. Three out of 100 admitted to taking narcotics permanently or occasionally. These patients require further evaluation and possibly anti-addiction therapy. Data from years 2005–2007 show that 11 % of people aged 50–64 and 6.7 % above 65 years of age are addicted to alcohol. More frequent addiction is noticed in men than in women; also patients with chronic illness drink alcohol in a high-risk way due to depression disorders (Wang and Andrade 2013). In addition, Egbert (2014) revealed that 10 % of people above 65 staying at home and 40 % in nursing homes meets the criteria for alcohol abuse. According to estimates, 55 million adults in the European Union (15 % of adult population) drink alcohol in amounts considered risky (MEMO/06/397, 2006). Data of WHO published in the 2012 report of 'Alcohol in the European Union. Consumption, Harm and Policy Approaches' revealed that Europe belongs to the regions of the world with the highest consumption of alcohol (Anderson et al. 2012). Together with the drug consumption discussed above, this suggests that the interaction of alcohol and drugs is inevitable.

Only 6 out of 10 respondents claimed that they receive the full amount of money to which they are entitled, and 4 out of 10 say that they do not receive the money are entitled to. This requires further studies, but it is also a justification for the need to pay more attention to the social situation, including the financial aspects of patients at primary care level. This is particularly important for the reasons of any possible financial abuse. In Poland, no complete statistics on violence in general and economic violence in particular exists. The latest information released from the Ministry of Labor and Social Policy contains the results of a research on domestic violence (physical, psychological, sexual, and economic). The analysis included 3,000 men and women over 18 years of age. Studies have shown that violence refers mostly to women (61 %). Women make up 70 % of the victims of economic violence, while men are the main perpetrators (68 %) (Report 2010). According to a study conducted in the United States, economic violence is closely linked to physical and psychological violence (Adams et al. 2008).

A low level of satisfied needs was reported more frequently in men, seniors, the ones who do not have a partner, as well as residents of rural areas. The same also concerns patients with a higher number of chronic diseases, a higher number of reported somatic symptoms, a high index of services, a high level of disease acceptance, a low level of satisfaction from health care, low levels of satisfaction with quality of health state, low quality of life in the Environmental, Psychological, Social Relationship Domains, and a high

level of quality of life in the Physical Domain. A low level of met needs was also found more frequently in patients with a low level of healthy eating habits, positive mental attitudes, preventive behavior, and a high level of health practices. It is worth noting that when the association between just two variables was studied such as the level of disease acceptance and Camberwell index or the quality of life in the Physical Domain and Camberwell index – a converse relationship was obtained compared with the result of logistic regression. Probably, the effect of other variables bears on these relationships.

It is possible that the results of the present study were influenced by the nature of the group investigated, i.e., patients with chronic respiratory diseases. However, similar correlations were found in a heterogeneous group of chronically ill patients in other studies (Kurpas et al. 2013). The level of unmet/met needs was related to gender and patients' marital status, and depended on healthcare services, satisfaction with quality of life, and health behaviors in particular having to do with positive mental and health prevention attitudes. In addition, low Camberwell index was related to lower quality of life in the Physical Domain in younger patients, to the lack of improvement in mental well-being during the past 12 months, to a greater number of medicines taken, higher education, and was present in patients who did not choose their family physicians by themselves. Moreover, Schoen et al. (2014) concluded that unmet needs were associated with lack of information in hospitalized patients discharged to home. Patients complained about not having received a written plan for follow-up care and that future checkups were not organized.

The level of satisfied needs in elder patients requires further analysis. Perhaps the significant factor might be to determine whether the range of needs is reduced with age or the elderly are less critical when assessing the degree of their needs fulfillment. In the present study, the level of education was not relevant to the degree of met/unmet needs. Some other reports are contradictory in this regard. Kurpas et al. (2013) have shown that patients with higher education tend to be more critical toward the needs fulfillment and critically evaluate the quality of care in primary healthcare.

5 Conclusions

The prevention program to increase the level of satisfied needs in patients with chronic respiratory diseases, apart from obviously being addressed to those with low levels of health satisfaction and quality of life indices, should be addressed to men, the elderly, those having no partner, living in the countryside, and having multiple somatic symptoms. Patients with a high level of disease acceptance, those maintaining physical quality of life and advantageous health behaviors should be considered as well. It should be emphasized that the comparison of subjective indicators of unmet needs among countries should be done with caution due to some differences in the reporting health needs, cultural differences, place of the health in the hierarchy of values and discrepancies between expectations and experiences in dealing with the healthcare system (Allin and Masseria 2011).

Conflicts of Interest The authors have no financial or otherwise relations that might lead to a conflict of interest.

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Pulmonary Rehabilitation in Advanced Lung Cancer Patients During Chemotherapy

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Abstract

The aim of this study was to investigate the utility of pulmonary rehabilitation for improving of exercises efficiency, dyspnea, and quality of life of patients with lung cancer during chemotherapy. After the enrollment selection, the study included 20 patients with newly diagnosed advanced lung cancer and performance status 0–2. There were 12 patients randomly allocated to the pulmonary rehabilitation group and another 8 constituted the control group that did not undergo physical rehabilitation. Both groups of patients had continual cycles of chemotherapy. Data were analyzed before and after 8 weeks of physical rehabilitation, and before and after 8 weeks of observation without rehabilitation in controls. The inpatient rehabilitation program was based on exercise training with ski poles and respiratory muscle training. We found a tendency for enhanced mobility (6 Minute Walk Test: 527.3 $\pm$ 107.4 *vs.* 563.9 $\pm$64.6 m; $p > 0.05$) and a significant increase in forced expired volume in 1 s (66.9 $\pm$ 13.2 *vs.* 78.4 $\pm$ 17.7 %predicted; $p = 0.016$), less dyspnea ($p = 0.05$), and a tendency for improvement in the general quality of life questionnaire after completion of pulmonary rehabilitation as compared with the control group. This report suggests that pulmonary rehabilitation in advanced lung cancer patients during chemotherapy is a beneficial intervention to reduce dyspnea and enhance the quality of life and mobility.

Keywords

Dyspnea • Exercises efficiency • Lung cancer • Lung function • Nordic walking • Pulmonary rehabilitation • Quality of life

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1 Introduction

Over the last decade, many studies supported the efficacy of pulmonary rehabilitation in patients with lung diseases, especially in chronic obstructive pulmonary disease (COPD), asthma, mucoviscidosis, and interstitial lung fibrosis. Pulmonary rehabilitation has become a recognized method of treatment (Nici et al. 2006) and is recommended by the Polish Society of Lung Diseases (Pierzchała et al. 2010), as well as international expert groups (Rabe et al. 2007). Therefore, it is proposed that pulmonary rehabilitation program should be introduced in cancer patients, based on the strategies established for patients with COPD, postulating that physical effort will improve physical activity and exercise tolerance, and will significantly decrease the level of dyspnea; thereby enhancing the health-related quality of life.

The hitherto consensus has been that oncological patients should not be subjected to rehabilitation training. Broadly defined physiotherapy has been considered an absolute contraindication for them. In 2010, the American College of Sport Medicine published the first recommendations on the usefulness of rehabilitation in cancer (Schmitz at al. 2010). The recommendations did not concern rehabilitation in lung cancer. The current state of knowledge is insufficient to answer the question of the relevance and influence of physical therapy in lung cancer patients. A review of the literature shows positive effects of physiotherapy in lung cancer after surgery (Jones et al. 2010, 2008; Spruit et al. 2006) and there seem to be a single only article that describes the results of rehabilitation in inoperable lung cancer during chemotherapy (Temel et al. 2009).

The currently used anticancer treatment, although extending the patient's life expectancy, is highly toxic. This situation has a bearing on the physiological and psychological state of patients. These effects lead to increased pain, loss of physical fitness and efficiency, increase fatigue, cause immune dysfunction, and reduce quality of life (McTieman 2004). Therefore, implementation of programs based on physical activity for reducing the above mentioned symptoms seems an attractive notion, particularly in view of overall beneficial effects of physical training reported in a number of meta-analyses. It has also been shown that physical training may reduce the risk of tumor recurrence, as well as it may extend life expectancy. Therefore, the aim of this study was to investigate the utility of pulmonary rehabilitation on exercises efficiency, dyspnea, and quality of life in patients with lung cancer during chemotherapy.

2 Methods

2.1 Subjects

The study was approved by the Ethics Committee of the Silesian Medical University (permission KNW/0022/KB1/184a/I/11/12 from 22.05.2012). There were initially 28 patients recruited for this study. All were diagnosed with stage III or IV lung cancer, or with an earlier stage of the disease but judged unsuitable for surgery or radiation. The diagnosis was set within the 6 weeks prior to the enrollment and was confirmed by cytology or histology. Of the 28 patients, five did not give final agreement to participate in the study, two were excluded from further proceedings due to rapid disease progression, and one patient died in seventh week of the rehabilitation program. Finally, 12 patients (10 men and 2 women; mean age 59 $\pm$ 7 years) were chosen to the rehabilitation group. In this group, ten patients were diagnosed with non-small-cell lung carcinoma (NSCLC) and two with small-cell lung cancer (SCLC). These patients were continually undergoing chemotherapy that was interspersed with the rehabilitation cycles (see below). The control group consisted of further eight patients with NSCLC stage III or IV. The group closely corresponded to the rehabilitation program group in terms of gender and age. The patients of the control group were assesses before and after 8 weeks of chemotherapy alone.

2.2 Methodological Highlights

Exercise capacity, pulmonary function, dyspnea, and a patient-reported survey of overall health and quality of life were investigated in the rehabilitation group, before and after completion of 8 weeks of rehabilitation. Physical rehabilitation was performed in 2-week cycles interspersed with consecutive rounds of chemotherapy with the cytostatic Platidiam-Vepesid. In the control group, which was not subjected to physical rehabilitation, the functional indices outlined above were compared before and after 8 weeks of chemotherapy alone (four consecutive rounds of the cytostatic).

Six-minute walk test (6MWT) was performed to assess exercise capacity. The test was conducted according to the 2002 ATS guidelines (Crapo et al. 2002). The test was performed twice in each patient. For the analysis, the best record was taken into account. The same rules were followed while performing the test in both rehabilitation and control groups. The basic estimated parameter was the distance covered during the test, expressed the absolute value of meters (m).

Pulmonary function was examined spirometrically using forced vital capacity (FVC) and forced expired volume in 1 s (FEV1) as performance indices (Jaeger-Masterlab; Erich–Jaeger GmbH, Wurtzburg, Germany). The results were normalized to the reference values proposed by the European Coal and Steel Community (Quanjer et al. 1993), and presented as a percentage of the predicted value (%pred.).

Dyspnea was assessed with the following scales. (1) Modified dyspnea scale of the Medical Research Council (MRC); (2) basic dyspnea index (BDI) describing dyspnea in five steps integrated into the following three categories: (a) Functional Impairment (FI), (b) Magnitude of Task (MT), and (c) Magnitude of Effort (ME); and (3) oxygen cost diagram (OCD). The methodological aspects of dyspnea rating and quantification using the methods above outlined have been described elsewhere (Jastrzębski et al. 2005).

A patient-reported survey of health and quality of life was conducted using a Short Form Health Survey (SF-36). The SF-36 questionnaire consists of 36 questions describing the state of health. It allows assessing of the physical quality of life – Physical Cumulative Score (PCM), which consist of 4 domains: Physical Functioning (PF), limits of, and difficulties in, physical functioning – Role Physical (RP), pain perception – Bodily Pain (BP), General Health (GH), and the mental quality of life consisting – Role Emotional (RE) and Mental Health (MH). The score ranges from 0 to 100; the higher the score the better the outcome is. The patients filled out the questionnaires individually. The methodological rules and the SF-36 data analysis have been described elsewhere (Jastrzębski et al. 2005).

2.3 Pulmonary Rehabilitation Program

Rehabilitation consisted of 8 weeks' physiotherapy program in the hospital environment. There were four 2-week rehabilitation cycles, each preceded by a round of chemotherapy. Therefore, each rehabilitation cycle was followed by a consecutive round of cytostatic treatment, followed, in turn, by consecutive 2 weeks of rehabilitation. Rehabilitation program ended after 8 weeks, before a consecutive round of chemotherapy. In two patients, the rehabilitation program was extended to 10 and 12 weeks. The control group of patients was observed without any physical rehabilitation.

Depending on the results of the initial 6MWT, the patients in the rehabilitation group were divided into 2 groups:

Group A – 6MWT >200 m (8 patients);

- Rehabilitation was conducted with the use of Nordic Walking, exercise was conducted once a day for 45 min at least 5 days a week, with a heart rate (HR) target of 70 % of predicted maximal HR (220 – age) ((HR = 70 % × (HRmax – HRsp) + HRsp)), oxygen saturation control during exercise (cut-off value ≤88 % SaO_2), and dyspnea (MRC scale <3);

- Aerobic exercises and respiratory exercises, once a day for 30 min, 5 times a week;
- Resistance training, once a day for 30 min;

Group B – 6MWT <200 m (4 patients),

- Exercise of respiratory muscles and peripheral muscles of upper and lower extremities (cycle ergometer); the program was determined individually.

2.4 Statistical Elaboration

Data were presented as means ± SD. The Wilcoxon Signed Ranks test, which does not require the Gaussian distribution, was used to compare baseline values of dyspnea, spirometry, and quality of life questionnaire with those after pulmonary rehabilitation. The results of 6MWT were compared with a *t*-test. A p-value of <0.05 was defined as statistically significant differences.

3 Results

Out of the 12 patients qualified for the rehabilitation program, 7 were evaluated after 8 weeks of rehabilitation, one after 12 weeks, one after 10 weeks, one after 6 weeks, and two after 4 weeks. Anemia and general weakness were the major factors affecting the shortening of the rehabilitation period. The mean time of rehabilitation in this group was 7.7 weeks. The control group consisted of 8 patients with the mean time of observation was 7.5 weeks (7 subjects were assessed after 8 weeks, one after 4 weeks). After pulmonary rehabilitation, no statistically significant improvement was observed in the 6MWT test, although the distance covered by the patients clearly tended to increase. The average distance was 527.3 ± 107.0 m and 563.9 ± 64.6 m before and after 8 weeks of rehabilitation, respectively. In the control group, the 6MWT distance was 502.8 ± 105.0 m and 509.4 ± 134.3 m before and after 8 weeks' observation time, respectively (Table 1).

In the rehabilitation group, there was a statistically significant improvement in FEV1 (66.9 ± 13.2 *vs.* 78.4 ± 17.7; $p = 0.016$) after completion of rehabilitation. In contrast, no significant differences were observed in FEV1 in the control group which did not perform physical rehabilitation (67.5 ± 26.1 *vs.* 70.3 ± 26.6; $p = 0.844$). The mean result of FVC showed no statistical increase in either group (Table 1).

MRC was the only dyspnea scale where there was observed a significant (1.3 ± 1.1 *vs.* 0.6 ± 0.5; $p < 0.05$) decrease in the rating of dyspnea after completion of rehabilitation. Conversely, in the control patients without physical

Table 1 Rating of dyspnea, six-minute-walk distance, and spirometry in the rehabilitation group before and after pulmonary rehabilitation and in the control group without physical rehabilitation

	Rehabilitation group			Control group		
Variable	Before PR	After PR	p-value	Before observation	After observation	p-value
MRC	1.3 ± 1.1	0.6 ± 0.5	0.047	1.4 ± 0.9	1.8 ± 1.3	0.313
OCD	2.0 ± 0.8	2.3 ± 0.9	0.375	1.6 ± 1.4	1.6 ± 1.3	0.999
FI	3.1 ± 0.9	3.2 ± 0.8	0.844	3.0 ± 1.1	3.0 ± 1.3	0.938
MT	3.3 ± 0.7	3.3 ± 0.8	0.999	3.5 ± 0.8	3.4 ± 1.1	0.562
ME	3.2 ± 0.9	3.6 ± 0.8	0.313	3.1 ± 0.8	3.3 ± 1.0	0.813
BDI	9.6 ± 2.3	10.0 ± 1.5	0.844	9.6 ± 2.1	9.6 ± 3.0	0.844
6MWT (m)	527.3 ± 107.4	563.9 ± 64.6	0.252	502.8 ± 105.0	509.4 ± 134.3	0.816
FEV1 (%)	66.9 ± 13.2	78.4 ± 17.7	0.016	67.5 ± 26.1	70.3 ± 26.6	0.844
FVC (%)	83.0 ± 16.3	89.6 ± 22.1	0.219	79.8 ± 23.1	81.8 ± 22.3	0.844

Data are means ± SD

PR pulmonary rehabilitation, *MRC* Medical RESEARCH COUNCIL questionnaire, *OCD* oxygen cost diagram, *FI* Functional Impairment, *MT* Magnitude of Task, *ME* Magnitude of Effort, *BDI* Basic dyspnea index (FI + MT + ME), *6MWT* six-minute-walk test, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity

rehabilitation a tendency for an increase in dyspnea was noticed (1.4 ± 0.9 *vs.* 1.8 ± 1.3; $p > 0.05$). The mean values of OCD were 2.0 ± 0.8 *vs.* 2.3 ± 0.9 and those of BDI were 9.6 ± 2.3 *vs.* 10.0 ± 1.5, before and after physical rehabilitation, respectively. These findings also pointed to a decrease in the sensation of dyspnea after physical rehabilitation, which, however, could not be statistically confirmed in the small sample of patients. In the control group, the mean values of OCD (1.6 ± 1.4 *vs.* 1.6 ± 1.3) and BDI (9.6 ± 2.1 *vs.* 9.6 ± 3.0) remained unchanged after the 8 weeks observation.

There also was a somehow greater increase in the Magnitude of Effort domain (3.2 ± 0.9 *vs.* 3.6 ± 0.8) in the rehabilitation group than that in the control group (3.1 ± 0.8 *vs.* 3.3 ± 1.0). A similar tendency was observed in Functional Impairment (3.1 ± 0.9 *vs.* 3.2 ± 0.8 in the rehabilitation group) and (3.0 ± 1.1 *vs.* 3.0 ± 1.3 in the control group). Concerning the Magnitude of Task, there was no change in the rehabilitation group, (3.3 ± 0.7 *vs.* 3.3 ± 0.8), but a tendency for increase in the control group (3.5 ± 0.8 *vs.* 3.4 ± 1.1) after the period of 8 weeks (Table 1).

The SF-36 general quality of life questionnaire showed a marked reduction in the perception of quality of life in all domains in both rehabilitation and control groups, with no statistically significant improvement after the completion of the 8-week long study protocol in either group (Table 2). The mean result of any domain hardly exceeded 50 points, and in about half of the domains it was in a range of 30 odd points. Despite the lack of appreciable improvement in the rehabilitation group, there was an upward trend in 8 domains (BP, VT, GH, RP, RE, SF, MH, and MCS) and a decrease in 2 domains (PF and PCS) there after physical rehabilitation. For comparison, the upward trend was observed in 2 domains (BP and GH) and a decrease in 8 domains (VT, RP, RE, SF, MH, MCS, PF, and PCS) in the control group that did not have rehabilitation.

4 Discussion

This study is one of the first randomized studies to examine the utility and benefits of hospital pulmonary rehabilitation program in patients with advanced lung cancer during chemotherapy. The principal finding of this study was the beneficial effect of exercise training on the mobility, feeling of dyspnea, and quality of life in the rehabilitation group. Surprisingly, the results demonstrate that rehabilitation in this group

Table 2 Rating of quality of life in the rehabilitation group before and after pulmonary rehabilitation and in the control group without physical rehabilitation

	Rehabilitation group			Control group		
Variable	Before PR	After PR	p-value	Before observation	After observation	p-value
PF	47.7 ± 17.7	45.3 ± 7.5	0.432	48.6 ± 10.9	45.5 ± 11.8	0.031
RP	34.1 ± 18.9	39.5 ± 12.9	0.625	46.5 ± 9.2	43.1 ± 10.6	0.437
BP	45.7 ± 14.2	46.3 ± 10.9	0.742	51.2 ± 11.2	53.7 ± 10.5	0.437
GH	35.7 ± 10.5	35.7 ± 9.2	0.625	44.0 ± 8.2	45.4 ± 8.7	0.687
VT	42.2 ± 18.9	48.0 ± 7.2	0.432	56.4 ± 10.7	50.5 ± 15.6	0.195
SF	33.8 ± 18.1	40.9 ± 12.0	0.233	50.0 ± 8.6	45.9 ± 13.0	0.098
RE	32.8 ± 22.5	38.1 ± 17.5	1.000	45.7 ± 10.0	43.1 ± 16.6	1.000
MH	36.3 ± 20.0	41.1 ± 13.4	0.492	47.9 ± 12.1	46.8 ± 11.5	0.687
PCS	44.2 ± 7.6	43.8 ± 7.3	0.846	48.5 ± 8.4	46.9 ± 10.1	0.383
MCS	38.0 ± 17.6	40.3 ± 10.0	1.000	49.3 ± 10.0	48.1 ± 10.8	0.641

Data are means ± SD

PR pulmonary rehabilitation, *PF* physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health, *V* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health, *PCS* physical cumulative score, *MCS* mental cumulative score

also had a positive effect on spirometric indices assessing lung function. To date, only a few studies have been published evaluating the outcome of pulmonary rehabilitation in patients with lung cancer (Spruit et al. 2006; Jones et al. 2008, 2010; Glattki et al. 2011). Overall, the authors failed to observe positive effects of rehabilitation on pulmonary function in patients with advanced disease. A notable exception is the paper by Glattki et al. (2011) who have reported a significant increase of FEV1 and FVC in patients who completed treatment (surgical or chemotherapy) and underwent rehabilitation. The authors investigated the effects of rehabilitation in a sizable group of 47 patients who exercised for 4 weeks 5 times a week. The rehabilitation program included breathing techniques, respiratory muscles training, and everyday training on a cycle ergometer for 25 min. The training intensity was comparable to that used in our present study. Those authors have reported that the distance in 6MWT increased after completion of rehabilitation; the increase amounted to 41 m, which was statistically significant. In that study, the effects of rehabilitation were evaluated in patients who completed cancer treatment, so that the patients were not exposed to negative effects of chemotherapy during rehabilitation. In contrast, in the current study we evaluated the effects of rehabilitation during uninterrupted chemotherapy. We found that the 6MWT distance increased by 37 m after completion of rehabilitation, which failed to reach statistical significance. This failure most likely stemmed from the meager size of our sample of cancer patients, just 12 subjects. In other studies, an even greater increase in the 6MWT distance has been found in lung cancer patients who had undergone thoracic surgery; from 63 m (Morris et al. 2009) to 99 m (Cesario et al. 2007).

Most authors evaluating the effects of rehabilitation in patients with lung cancer would consider a decrease of the feeling of dyspnea and improvement of quality of life as sufficient reasons to implement this type of medical intervention (Aaronson et al. 1993) So far, only the study by Temel et al. (2009) evaluated the effects of 8-week rehabilitation in patients with newly diagnosed advanced NSCLC during chemotherapy. In the years 2004–2007, 25 patients were enrolled into the study, of who only 11 (44 %) completed the entire rehabilitation program. The authors used the aerobic training and weight training for 90–120 min twice a week. The results demonstrate an increase in 6MWT, which similar to our present study failed to reach significance. Likewise, there is a greater score in many a domain of SF-36 questionnaire, but no statistically significant improvement of quality of life after completion of rehabilitation was noted. However, in the Lung Cancer Subscale, a questionnaire specific for lung cancer, those authors have reported significant improvement. Similar to the present study, Glattki et al. (2011) have found a significant decrease in the sensation of dyspnea on the MRC scale.

The present study has got limitations. The study could not address the essential issue, i.e., whether pulmonary rehabilitation prolongs the life of cancer patients. The sample of lung cancer patients was small. However, we chose to limit the study sample only to those with advanced disease, given the potential benefit of the intervention in severely morbid patients. A large dispersion of data makes it impossible to determine which domains of quality of life actually improve as a result of rehabilitation. Our exercise program was quite intense, requiring everyday sessions for up to 2 h. A modification of the exercise program toward less frequent, less intensive, or perhaps home-based could be more acceptable for patients with advanced lung cancer. Eight weeks of rehabilitation seems to be too long for some patients. According to our experience, each patient should be reviewed after 2 weeks of rehabilitation so that the following 2 weeks of rehabilitation could be modified according to individual abilities. In addition, the study took place in an academic medical center, and the findings may not be generalized to patients with advanced lung cancer seeking oncology care in the community. Lastly, we did not collect information on why some patients, who were offered to participate in the study, opted out of it.

On the positive side, the strength of the present study is that rehabilitation was supervised, which, in contrast to home-based programs, ensured not only the safety of severely ill participants but also the accuracy of adherence rate. We included a well-defined homogenous population of patients with a newly diagnosed advanced lung cancer. Our intervention included Nordic Walking, which is easy to perform and economical for physical activity. Patients trained in Nordic Walking can continue that form of activity in home-based rehabilitation. Lastly, improvement in symptoms and quality of life can prove critically important when the long-term survival is not an outcome that can be influenced by physical rehabilitation.

Controlled clinical trials are necessary to better define the benefits and to optimize the intervention. We believe the findings of the present study, as limited as they are, have practical implications since they demonstrate that pulmonary rehabilitation is feasible in advanced lung cancer during chemotherapy, and it has the potential to improve quality of life and mobility of patients. Therefore, we advocate a more widespread use of pulmonary rehabilitation in lung cancer patients.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Ondine's Curse – Genetic and Iatrogenic Central Hypoventilation as Diagnostic Options in Forensic Medicine

Robert Susło, Jakub Trnka, Jacek Siewiera, and Jarosław Drobnik

Abstract

In the Nordic mythology a man lost his ability to breathe without remembering it after he was cursed by water nymph - referred to as 'Ondine's curse' – and then he died as soon as he fell asleep. Family medicine specialists are familiar with many sleeping disorders that their patients commonly call by the term Ondine's Curse. In medical sciences this term is historically related to the group of conditions that have as the common denominator seemingly spontaneous onset of life-threatening hypoventilation. The physiology and genetics specialists focus mainly on congenital central hypoventilation syndrome (CCHS), which was proven to be linked to several genetic mutations. Anesthesiologists tend to be more interested in similarly manifesting iatrogenic condition. Typically, patients that were previously subjected to general anesthesia, after temporarily waking up and regaining the spontaneous respiratory drive, later fall back into unconsciousness and develop hypoventilation. Anesthesiologists also call it Ondine's curse because of the sudden and unexpected sleep onset. The iatrogenic Ondine's curse is proven to be precipitated by delayed anesthetics release from patients' fat tissue – where it was deposited at the time general anesthesia was administered – back into bloodstream. Forensic medicine has to consider the latter form of Ondine's curse called scenario more often, as they investigate sudden

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deaths related to surgery and general anesthesia in the post-operational care period. These cases may also fall into the category of medical malpractice-related deaths.

Keywords
Anesthesia • Medical law • Respiration disorder • Sleep apnea • Sleep disorder

1 Introduction

The name Ondine's Curse or Ondine's syndrome, is rooted in the Nordic mythology. It refers to Ondine, a water nymph having beautiful womanly shape. According to the myth once Ondine fell in love with a man whom she later cursed because he did not remain faithful to her. It made the man unable to breathe spontaneously, without remembering about it, so that he could survive only while staying conscious, but once he eventually fell asleep he stopped breathing and died.

The term Ondine's curse is used occasionally in forensic medicine in the context of breathing arrest when no clear clinical diagnosis is established. It must be stressed that this term has now rather historical connotations. It is still being used due to its high descriptive power, bringing up rich associations in lawyers, rather than because of its actual clinical usefulness which seems limited. Therefore, the term Ondine's curse keeps appearing from time to time in medical files as a bit mysterious piece of jargon rather than valuable clinical diagnosis. Medical scientists use this term in cases of respiratory tract or nervous system-related symptoms leading to respiratory arrest, which causes were not fully determined. Ondine's curse should currently be considered not as a diagnosis, but rather as a constellation of symptoms that are common to various pathologic states of completely different etiology. The typical symptoms of Ondine's curse in some patients appear to be coexisting with some rare genetic variants, but also may be related to several iatrogenic conditions, medical treatment complications, and even mistakes in medical care – such cases often become subjects to lawsuits and court trials. It does not matter what the etiology of Ondine's curse is in a given patient, the common denominator of all such cases are symptoms of hypoventilation in a sleeping or unconscious patient, leading to acute hypoxia and sometimes death. That is true both for case reports in medical literature and for law-related expertizes. It should be remembered that quite often the term Ondine's curse is associated with any clinical situation manifesting as sleep disorder of some kind or just increased sleepiness, which is often confusing to family doctors.

2 Methods

The study was approved by a local Ethics Committee of the Medical University of Wrocław, Poland. The aim of the study was to select – on the basis of the available medical literature and papers and the expertizes issued by the Department of Forensic Medicine of the Medical University in Wroclaw, Poland, within the years 2002–2010 – the already known scenarios of Ondine's curse and its definitions circulating among medical personnel and patients. The archived expertizes reviewed enabled to find the cases in which teams of experts have considered the possibility of improper medical treatment in patients that developed acute hypoventilation-related respiratory insufficiency that coexisted with sleep or consciousness disturbances. The chosen cases were reviewed and interpreted along the current medical knowledge – especially they were

compared against the up-to-date criteria of the genetic hypoventilation syndromes, iatrogenic conditions, and intoxication-related ventilation disturbances.

3 Results and Discussion

In the medical literature and papers the term Ondine's curse is used in different contexts: as a genetic condition, as a disturbance resulting from central nervous system lesions, as a cause of the death related to substance abuse, and as a complication of general anesthesia.

According to some authors (Gozal 1998), the term Ondine's curse is commonly used to describe rare neurological complications of medical treatment, defined as life-threatening disorder manifested primarily as respiratory insufficiency in association with sleep, together with hypoxemia and impaired reaction in ventilation to the presence of elevated blood carbon dioxide. Several case reports found in medical papers refer to Ondine's curse as a set of disturbances resulting from neurosurgical procedure in patients ill with tumors of cervical spine or vertebral column. One of such cases described a 2 years old female child patient showing ventilation disturbances coexisting with consciousness loss after excision of cervico-medullary tumor – ganglioglioma. The neurosurgical procedure was carried out successfully, but in the early postoperative period the patient's lower cranial nerves and cerebellum functions deteriorated and she suffered from hemiparesis. The patient returned to the proper neurologic state within several months, but she was also diagnosed with mild sleep apnea, referred to as Ondine's curse. There were recurring severe cyanotic breath-holding spells that continued several times per day with rapid onset and progression of hypoxemia, loss of consciousness, sweating, severe generalized and prolonged muscle contraction. In the beginning those spells were hard to control with medications, but 5 months after the surgery a portable monitor of oxygen saturation, equipped with an alarm in case of critical hypoxemia level helped the patient to recover to the extent that she could leave the hospital (Fujisawa et al. 2005). Similar set of symptoms, also referred to as Ondine's curse, was described in an adult female patient admitted to the hospital for diagnostic of relapsing acute severe central hypoventilation, coexisting with trigeminal and glossopharyngeal neuralgia. Although the symptoms she presented with were almost identical to those present in the 2 years old girl case, the patient was diagnosed with medullar capillary telangiectasia and was successfully treated with diaphragmatic pacing system placement (Kapnadak et al. 2010).

Among specialists in genetics and pediatricians, the term Ondine's curse is most commonly associated with the central congenital hypoventilation syndrome (CCHS) which has a genetic background (Trochet et al. 2005; Gaultier et al. 2004; Hamilton et al. 1989). It has been shown that the Phox2b gene, which is necessary for proper autonomic nervous-system development, is altered in most CCHS patients. The CCHS often coexists with many other central nervous system disturbances or with other genetic abnormalities, especially neuroblastoma and Hirschsprung disease (Gaultier et al. 2005). In one study, patients suffering from CCHS have been reported to be extremely hypersensitive to ethanol, narcotic drugs, and other common substances of abuse (Chen et al. 2006). In the case of 4 years old girl diagnosed with CCHS and Hirschsprung disease, the anesthesiologist, knowing the elevated risk of applying general anesthesia, decided to use sparingly only anesthetic gases. This allowed performing the needed dental surgery and did not interfere with regaining spontaneous ventilation already within 18 min after the end of the anesthesia. As only sevoflurane was used, no hypoventilation or apnea appeared after the surgery, which could otherwise develop due to prolonged effects of opioids, preoperative sedatives, anxiolytics, muscular relaxants, and intravenous anesthetics (Ishibashi et al. 2004). Another patient, an adult Caucasian male suffering from CCHS, who underwent general anesthesia, did not end up so well. His waking up process was delayed and the respiratory function needed prolonged support,

the breathing impairment was likely caused by the use of opioids (Wiesel and Fox 1990). Nowadays, it is possible to avoid such anesthesia complications mainly by using modern opioid analgesic instead of morphine. One of them, called remifentanyl, has been used in a 50 years old woman diagnosed with CCHS. Due to the compound's very short half-life time in human organism, it can be used effectively as a continuous intravenous drip. When the drip is done with, respiratory drive reverts to the normal level almost instantaneously, even in CCHS patients (Niazi et al. 2011).

Patients with Phox2b mutation associated with CCHS, due to advanced sleep monitoring techniques and non-invasive sleep apnea treatment, are now capable of surviving the childhood and follow the standard educational pathways. Little information is available on the exposure of CCHS patients to substances of abuse, including ethanol and typical or atypical narcotic drugs. As these substances are commonly used and abused in modern everyday life, they can also interfere with patients' health status in unpredictable and potentially dangerous ways, particularly considering their spreading use among schoolchildren. It has not yet been investigated whether or not the hydrocarbons present in the environment constitute a serious health threat to children suffering from CCHS and what concentration should be considered dangerous. In case of unexplained children deaths, especially those with antecedent breathing disturbances, not only extended toxicology screening but also DNA analysis for the presence of Phox2b gene might be suggested. Forensic investigation of a possible link between the death of a CCHS patient and environmental toxic exposures would be difficult as inhaled hydrocarbons inhalation migrate almost immediately from the blood to target tissues, which are the brain and fat, the tissues that are not routinely included into the standard toxicological screening. Similarities in the depressive mechanisms of action on the central respiratory control of ethanol, narcotic drugs, other common substances of abuse, but also some prescription drugs, suggest that the CCHS patients may be vulnerable to a spate of chemical compounds, including analgesic and anesthetic drugs administered during life-saving medical interventions. The use of modern opioid analgesics such as remifentanyl, during anesthesia, should become the gold standard in patients with established risks of respiratory problems, such as history of anesthesia-related complications or acute hypoventilation in the post-operative period, since it minimizes the risk of prolonged depression of respiratory drive. Unfortunately, there is currently no fully effective method that allows predicting and preventing the prolonged general anesthesia-related respiratory depression in non-CCHS patients. The lack of technical means to control the influence of anesthetics results in an insufficient understanding of the nature of respiratory disturbances and their influence on the patient's consciousness. In the early times of anesthesia evolution and even later in the second half of the twentieth century the uncontrolled recurrence of general anesthesia after the patient had already temporarily regained consciousness has been known to medical personnel under the commonly used name of Ondine's curse. This phenomenon is now known as the postoperative respiratory failure and is defined as the need for continued mechanical ventilatory support beyond 48 h after surgery, which may require re-intubation if the endotracheal tube has already been removed (Atchabahian and Leibowitz 2005).

In the neurological literature the term Ondine's curse is used in the context of respiratory disorders developing in patients with central nervous system dysfunctions - primarily caused by anatomical lesions in the areas of the brainstem essential for respiratory control (Schläfke et al. 1975). This term also is sometimes used among drug addicts to describe situations when the abused substances cause sudden respiratory arrest and death. Cigarette lighters were known as convenient tools of abuse for many years, but the most commonly considered mechanism of poisoning was rather swallowing the fuel than inhaling it (Mirkin 2007). Recently, it turned out that volatile hydrocarbons composing the lighter fluid – including benzene, propane-butane, hexamine,

lacolene, and naphtha – are being commonly abused, mainly by youths. They may be inhaled by the abusers directly from the containers or indirectly from under a polythene bag-made tent to achieve a high state typical for many substances of abuse. The volatile hydrocarbons can also be retrieved form refueling containers of cigarette lighters, which can be possessed legally also by youths, or containers with "compressed air". The latter were designed for cleaning of electronic devices from dust, but the pressurized gas they contain is anything but pure air; it rather is a high concentration of various hydrocarbons mixed with other inert gasses, like R134a or R152a. It has been reported that in cases of fatal intoxication, apparently healthy individuals fall into cardiopulmonary arrest and die immediately after inhalation, whereas chronic abusers may suffer no harm. In such cases autopsies reveal no characteristic macro- or microscopic signs and the determination of the cause of death is possible only on the basis of toxicological investigation. The investigation should be based on facts known from the medical history. Specimens of brain and fat tissue, which are not routinely tested, are notably helpful in such cases. Such specimens are collected and preserved when circumstances of the death are unclear and are subject to a judicial or official inquiry (Tomczak et al. 2012; Nowicka et al. 2011; Gross and Klys 2002).

The interest of forensic medicine in Ondine's curse emerges from analyzing peri- and postoperative anesthesiology complications. Ventilation with altered proportions of gases (Marczak and Pokorski 2004) as well as many drugs used during general anesthesia are known to influence central respiratory chemosensors (Pokorski et al. 1981) and ventilatory chemoreflexes (Pokorski et al. 1989). In the practice of forensic medicine it is common for pathologies or functional disturbances of respiratory tract organs to be directly responsible for the patient's death (Trnka et al. 2013), but Ondine's curse cases do not fully fit into this narrow scheme. The case of multiple medical errors, chosen to be reported in this article, was evaluated by a team of experts from the Department of Forensic Medicine of the Medical University in Wrocław, Poland. They issued two successive expertizes, in the years 2002 and 2003. The analysis of the case files revealed that the patient, a 28 years old pregnant woman, arrived at the admission room of the gynecology and obstetrics hospital in an early stage of properly timed natural delivery. Her previous pregnancy was terminated by planned Caesarean section and it was the main basis to carry out next Caesarean section. The patient insisted on being subjected to general anesthesia during the procedure and did not accept the option of subarachnoid or subdural anesthesia, which was strongly suggested as an optimal procedure by an anesthesiologist on duty. The anesthesiologist considered her general composure, overweight and short neck, as a possible predicament for effective general anesthesia. Indeed, there were minor problems during placing the endotracheal tube, resulting from the difficulties with the larynx visibility, resolved by using a Bougie lead. The subsequent Caesarean section was carried out successfully, no medical complications were registered at the operating room and the devices monitoring life functions showed no abnormalities. However, the endotracheal tube was not removed immediately after the surgery because of recent history of "difficult intubation". After the surgery the patient managed to wake up partially for a moment. Yet she became unconscious again when she was trolleyed in the horizontal position to a post-operative room, located just 3 m away, accompanied by the anesthesiologist, one of the operation theater nurses, and a midwife. The anesthesiologist left the patient at the door of the post-operation room, handing over to the midwife the patient's health status card with dispositions which needed to be carried out in the post-operation room. The assisting nurse and the midwife moved the patient from the trolley onto the hospital bed, and then the nurse left heading back towards the operating theater. The midwife was the only staff member assigned to the post-operation room. As soon as she attached the monitoring devices to the patient's body, the alarm sounded, triggered by hypoxic arterial blood oxygen saturation of 78 %. The midwife first tried to "wake

the patient up to make her breathe" by calling her by the name and moving her, but it was to no avail. The midwife, as instructed by the anesthesiologist, started passive oxygen therapy by attaching oxygen line via a connector to the endotracheal tube, with the gas flow rate adjusted to 3–4 l per minute. During exchanging an empty intravenous drip and checking the kind of fluid that should be administered the midwife looked back at the patient and noticed that she turned purple and "was swelling rapidly". The midwife immediately detached the oxygen line, attached the AMBU bag and started ventilation. Since the anesthesiologist on duty was at that moment unreachable, the midwife continued AMBU ventilation, but the patient's condition worsened, with the abdomen protruding more and more, and patchy brown-violet discolorations appearing on the face and upper limbs. It took 3 min from the first symptoms of cardiorespiratory collapse, until the patient was moved to the local intensive care unit (ICU), where she was diagnosed with subcutaneous emphysema of chest and abdomen, neck, head, and both upper limbs, coexisting with massive bilateral pneumothorax and pneumoperitoneum. The air was effectively evacuated from both pleural cavities, but the patient remained deeply unconscious, presenting with asymmetric pupils, pathologic neurolgical reflexes in lower extremities, and weakened reflexes and muscle tension in all extremities. Computed tomography revealed brain edema and multifocal ischemic lesions of the brain's frontal lobes. The patient's life was rescued; she regained consciousness and survived. However, she has never fully recovered. Despite of months of rehabilitation, she remained physically and psychologically debilitated, functionally limited to perform only very basic everyday tasks and with deep personality and emotional disturbances.

The case of a young pregnant woman presented above is life-threatening central hypoventilation as a sequel of postoperative respiratory insufficiency and critical hypoxia. This is, in a sense, an example of the importance of Ondine's curse to both clinical and forensic medicine practice. The first expertize in the case suggested an accidental rupture of the trachea as the sole source of subsequent complications leading to the development of subcutaneous emphysema; the tracheal damage due possibly to the difficult intubation. This kind of explanation and three other kindred expertizes did not convince the prosecutor involved in the case as the tests performed revealed no tracheal rupture, and the aspects of the case remained inexplicable. In the end, additional expertize was requested from the forensic team. The in depth analysis allowed redefining the final interpretation of the case scenario and resulting responsibility of the medical staff. The complications that followed were described as stemming from the phenomenon of Ondine's curse following general anesthesia, as the patient never regained full consciousness in the operating room after the surgery had finished. There was just a brief period of independent ventilation, after which the patient fell back into unconsciousness, with fast progressing hypoventilation. Arterial blood oxygen desaturation was not monitored during transportation from the operation to post-operation room, which took likely much longer time than needed as judged from the direct vicinity of the two rooms. Therefore, the patient arrived at the post-operation room in deep hypoxia which started the chain of events leading to the tragic outcome. Moreover, additional questioning by the prosecutor revealed that the midwife had no prior experience at her current workplace and she came back from long maternity leave just days before the complication occurred. She reacted in a seemingly reasonable way, attaching the oxygen line to the endotracheal tube as soon as possible. Unfortunately, being in stressful haste, she made a fatal mistake attaching the high pressure oxygen line ending with a Y-shaped connector to the endotracheal tube, of which the second Y-arm was occluded by a stopper. The patient was then literally bloated with oxygen, which produced massive subcutaneous emphysema, bilateral pneumothorax, pneumoperitoneum, and multiple gas emboli of the brain, causing, in turn, multiple ischemic foci, especially in the frontal lobes of the brain and in the brainstem. On the other hand, this connector was kept improperly in the post-operation room, with no

respirator attached. The Y-type connectors are routinely used to interconnect endotracheal tubes with respirators, with a side branch used to evacuate the fluid occasionally accumulating in the bronchial tree, and therefore the side branch is most of the time occluded. The patient should have had a T-type connector attached, with a side branch open to the atmosphere allowing the excess of gas out during the installation of one-directional oxygen flow. Thus, there were multiple mistakes made in this case. The anesthesiologist breached the rules of good medical practice, deserting the patient known to be at high risk of developing respiratory insufficiency or relapse of respiratory depression after surgery. The risk stemmed from the possibility of delayed release of anesthetic compounds from the patient's fat tissue or discrepancy between the elimination rate of anesthesia, which typically has long lasting effects, and the anesthetic antidotes administered after surgery to wake the patient up, whose effects wear out much faster. The anesthesiologist is the main person responsible for the patient until he regains wakefulness. In addition, however, there were other co-responsible members of the medical staff involved in the multi-layer systemic medical errors. Among them, there were the midwife who erroneously attached the oxygen line, the chief of nursing staff who failed to train the midwife at the new workplace, the chief of the ward who was aware of improper equipment in use and who failed to replace it. All those persons should be more cognizant of their duties as the medical professionals.

In the patient case described above, there was no earlier history of apnea or ventilation disorder of any kind prior to the Caesarean section. The patient insisted categorically on, and gave written consent for, being subjected to general anaesthesia during labor, after being informed about the possible difficulties with intubation. Consenting to anesthesia-related procedures in writing is obligatory to keep the anesthesiologist's action legal (Siewiera et al. 2013).

Symptoms of Ondine's curse during pregnancy and after delivery – defined as unexplained hypoxia associated with sleep disturbances – are not uncommon. For instance, there is a report of hypoventilation tied to sleep disturbances in a 34 years old woman in the 3rd trimester of second pregnancy (Ochoa-Sepulveda 2005). The pregnancy, similar to the first one, was complicated by generalized edema and high blood pressure. From the 25th week of pregnancy on, these symptoms were accompanied during sleep by intermittent brief periods of apnea, lasting up to 1 min. The husband use to wake her up each time he noticed a prolonged episode of breathlessness. She displayed no pathological signs after being woken up. From the 29th week, apneic episodes became severer and in the end she needed respiratory support and an emergency Caesarean section. The patient was unable to breathe spontaneously for 2 weeks after surgery, after which time the breathing difficulties gradually subsided. Two years earlier, the patient's first vaginal delivery had also been associated with apnea. At that time breathing disorders appeared immediately after delivery, the patient was intubated, but breathing difficulties resolved spontaneously, so that the endotracheal tube was removed within 4 h.

In the medico-legal discussion of potential causes of acute apnea there are two other conditions mentioned in medical literature as related to Ondine's curse symptoms: lesions secondary to ischemia of the brain and iatrogenic circulatory insufficiency resulting from critical intracranial blood pressure variations. Ischemic brain lesions resulting in Ondine's curse without any other symptoms have been described in the case of spontaneous isolated stroke in the medulla oblongata (Juan et al. 1999). In the case described in the present article, the cause of multiple brain lesions was the air that has entered the blood vessels in the lungs that ruptured due to increased air pressure. Such a situation in case of the patient's immediate death is likely to manifest as the presence of bubbles of air in the arteries and veins on the brain surface. A quite similar case was reported concerning the 72 years old female patient subjected to the procedure of sub-occipital cranial decompression, who in the postoperative period developed hypoventilation referred to as Ondine's curse (Gupta et al. 2003).

In case of Ondine's curse symptoms related to death or health loss, the forensic expertizes should find out the initial cause of acute hypoventilation and respiratory insufficiency since it is needed for the medico-legal interpretation by prosecution or for civil medical malpractice lawsuits. The most important question that needs to be answered is then whether or not the hypoventilation-related hypoxia could have been predicted, and thus effectively prevented. The answer to this question is different in case of chronic progressing neurologic illness that could have been overseen in the preoperative diagnostic process, in case of rapid onset of unpredictable complication of general anesthesia, or in case of predictable and potentially fully reversible condition associated with general anesthesia, which the medical staff should be aware of. In the context of the case evaluated in the present article, it is sometimes difficult in practice to identify the case as associated with Ondine's curse, to find its primary cause, and then to address the question of medical personnel's possible legal liability.

4 Conclusions

The term Ondine's curse is currently outdated and should be avoided in medical official documents as it refers to a set of symptoms that in different cases may be of substantially different etiologies. In cases evaluated by forensic medicine, acute central hypoventilation is more likely to result from complications of general anaesthesia than to be associated with congenital central hypoventilation syndrome (CCHS). The differential diagnosis during forensic investigations of suspicious death causes in the postoperative period should include the possibility of spontaneous or iatrogenic complications leading to hypoventilation. Establishing the CCHS as the cause of death in previously undiagnosed patients may be extremely difficult. Thus, cases of unexplained death preceded by breathing disturbances should be evaluated with extensive analysis of medical history and all available medical files, full autopsy, extended toxicology screening, and possibly also DNA testing for Phox2b mutation. All hypoxia cases resulting from central hypoventilation following surgery performed under general anaesthesia should be evaluated by forensic medicine to eliminate the possibility of medical errors.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Pulmonary Function Abnormalities in Regard to Age at the Time of Diagnosis of Hypersensitivity Pneumonitis

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Abstract

Hypersensitivity pneumonitis (HP) is a complex syndrome caused by exaggerated immune response to inhalation of a variety of organic particles in susceptible individuals. In this study we assessed the relationship between age at the time of diagnosis and the degree of functional and radiological changes in HP. The diagnosis of HP was made on the basis of a combination of clinical symptoms, medical history, serological tests, radiologic evidence of diffuse lung disease, and absence of other identifiable causes of lung disease. We reviewed the records of 111 patients (68 women) diagnosed with HP over a period of 18 years (1995–2013). The patients were stratified into 3 age-groups: <30, 30–49, and ≥ 50 years old. The commonest cause of HP was avian antigens (56.8 %). Dyspnea was present in 97.3 % of patients, weight loss in 54.7 % of patients, and respiratory insufficiency in 24.3 % of patients. Lung fibrosis in chest computed tomography was found in 35.1 % of patients. Lung function was impaired more seriously in the youngest age-group, with lung diffusing capacity for carbon monoxide (DLCO) <40 % in 69.2 % of these patients. Restrictive pattern was present in 92.3 % of patients in this group, as compared with the 41.0 % in the whole cohort. In this group, desaturation in the six minute walk test also was most notable, amounting to a median of 11 %. In conclusion, diagnosis of HP at young age is predictive of a more severe clinical course of disease, with lung fibrosis and higher disturbances in pulmonary function.

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Bird fancier's lung • Diffusion capacity • Extrinsic allergic alveolitis • Interstitial lung disease • Lung disease • Pulmonary function • Total lung capacity

1 Introduction

Hypersensitivity pneumonitis (HP) is a complex syndrome caused by exaggerated immune response to inhalation of a variety of organic particles in susceptible individuals. The true prevalence of HP is difficult to ascertain. Data from European surveys suggest that HP constitutes 4–15 % of all interstitial lung diseases (Lacasse et al. 2012; Hanak et al. 2007). HP is the third common cause of interstitial lung disease in Poland, after idiopathic pulmonary fibrosis and sarcoidosis. The disease occurs worldwide in a variety of occupational, home, and recreational environments (Selman et al. 2012). The offending antigens can be classified in five broad categories represented by disease prototypes: bacteria (farmer's lung), fungus (summer-type HP), mycobacteria (hot-tub lung), proteins (bird fancier's lung, BFL), and chemical products (Lacasse et al. 2008). Despite a large number of individuals exposed to potential HP-causing antigens only approximately 5–15 % of them develop the disease. It depends on individual susceptibility and on the type, intensity, and duration of exposure to the causal agent, smoking habits, and other factors. Environmental co-factors, such as viruses or host's genetic and immune vulnerability, may underscore the variability in disease course and response to treatment (Agache and Rogozea 2013; Fink et al. 2005). For example, only ~3.4 % of budgerigar fanciers, 8 % of pigeon fanciers, and 4.3 % of farmers develop HP. A much larger number of subjects exposed to the antigen develop sensitization in the form of a humoral or cellular immune response, but do not progress from sensitization to overt disease (Agache and Rogozea 2013). The most commonly implicated antigens are bird proteins, thermophilic actinomycete species, fungi, and some low-molecular-weight chemicals that combine with host proteins to form haptens. As of now, above 200 such agents are renumerated (Selman 2004; Bourke et al. 2001). Cigarette smoking is less prevalent in patients with HP than in the general population. In fact, smoking seems to be protective against development of HP (Costabel et al. 2012). There is a lower incidence of precipitating antibodies in smoking population (Selman et al. 2010). In smokers, however, the disease is associated with more severe course and higher mortality (Hirschmann et al. 2009). The pathogenesis of HP is complex and still poorly understood. The disease combines type III and IV reaction with granulomatous inflammation. It is pathologically characterized by interstitial mononuclear cell infiltration, poorly formed nonnecrotizing granulomas, cellular bronchiolitis, and fibrosis (Selman et al. 2010).

There is no specific test for HP. Diagnosis is made on the basis of a high index of suspicion, clinical history, physical examination, laboratory test results, pulmonary function testing (PFT), and imaging studies (Cardoso and Carvalho 2014; Wells et al. 2008). The recommendations of several diagnostic criteria for HP have been published (Terho 1986; Richerson et al. 1989; Cormier and Lacasse 1996). The most widely used are those proposed by Richerson et al. (1989) which include history, physical findings, pulmonary function test indicating an interstitial lung disease, consistent x-ray film, known exposure to a recognized antigen, and antibodies to a known antigen. In 2003, a panel of experts tried to establish clinical criteria of the HP diagnosis (Lacasse et al. 2003), but it remains difficult and must be supported by additional tests. HP is typically classified, on the basis of

clinical presentation, as acute, subacute, or chronic, depending on the intensity, duration of exposure, and the level of host reactivity (Selman 2004; Richerson et al. 1989). This classification had been proposed before the use of computed tomography to describe HP (Lacasse et al. 2008). There is still a lot of confusions and propositions concerning a new HP classification (Lacasse et al. 2012). Depending on the dynamic nature of the disease, it can be classified as acute progressive, acute intermittent non-progressive, or recurrent non-acute disease (Cardoso and Carvalho 2014; Girard et al. 2009).

Dyspnea, cough, flu-like syndrome, and weight loss are common, but not pathognomonic symptoms for HP. However, weight loss with low BMI may be a prognostic factor. Chest radiography, an initial step in the investigation of patients presenting symptoms suggestive of HP, may be normal up to 12–20 % of individuals, especially in subacute disease. High resolution computed tomography (HRCT) is much more sensitive; only 2 % of patients do not have image changes. The presence of air trapping in combination with centrilobular nodules and ground-glass opacification is a classical combination suggestive of HP. Ground glass opacification is found in similar percentages in the acute, subacute, and chronic form of BFL. Air trapping is predominately seen in the acute and subacute phases rather than the chronic phase (Chan et al. 2012). The HRCT findings of fibrosis are the following: irregular linear opacities, traction bronchiectasis, lobar volume loss, and honeycombing. Radiographic fibrosis predicts worse outcome in patients with HP. The combination of reticulations on CT scan and crackles on lung examination may identify patients with a particularly poor outcome (Mooney et al. 2013).

Lung function abnormalities play an important role in determining the severity of the disease, but they do not differentiate HP from other interstitial lung diseases. They are useful to evaluate the physiologic abnormalities and the associated impairment. The results may be helpful to select those in whom corticosteroids may be justified. HP patients show a restrictive ventilatory defect. However, because HP affects the small airways, a mixed obstructive/restrictive functional pattern may be observed in some patients. An early reduction of diffusing capacity for carbon monoxide (DLCO) is often found. Some HP patients exhibit hypoxemia at rest. Patients with mild-to-moderate disease may be normoxemic at rest, but oxygen desaturation is usually observed with exercise (Lacasse et al. 2012; Selman et al. 2012). Unlike previous studies regarding patients with HP, this study concerns pulmonary function according to the age at the time of HP diagnosis. We observed patients in whom HP was diagnosed over 50 years back and much younger patients. These younger were more severely ill.

2 Methods

2.1 Study Population

The study was conducted in accordance with the ethical standards of the Helsinki Declaration for Human Experimentation. We retrospectively reviewed medical records of 111 consecutive, mostly untreated, patients (68 women and 43 men) over a period of 18 years (1995–2013), referred to the Third Division of Pulmonary Diseases of the National Tuberculosis and Lung Diseases Research Institute in Warsaw, Poland. The records were examined to gather clinical, radiologic, and pulmonary function data at the time of diagnosis of hypersensitivity pneumonitis. The patients were stratified into the following age-groups: <30, 30–49, and >50 years of age. The diagnostic criteria according to Lacasse et al. (2003) included the following: (1) episodic or persistent respiratory symptoms; (2) radiologic evidence of diffuse lung disease, (3) known exposure or positive serum precipitin test to an inciting agent, and (4) no other identifiable cause for lung disease. In the absence of identifiable exposure to a causative antigen or positive serologic test, one of the following two criteria was required for inclusion in the study: (1) transbronchial or open lung biopsy that demonstrated features of HP and

(2) bronchoalveolar lavage (BAL) lymphocytosis (≥30 % for nonsmokers and ex-smokers or ≥20 % for current smokers) in combination with the corresponding HRCT findings (Hanak et al. 2007).

Serological testing was performed according to the method of Ouchterlony (1953). Serum precipitins were investigated by agar gel double diffusion. The antigenic panel included *Thermopolyspora polyspora, Erwinia herbicola, Aspergillus fumigatus*, and avian dropping extracts (pigeon, turkey, duck, chicken, goose, and parrot).

2.2 Pulmonary Function

All patients underwent a functional evaluation that included spirometry, whole-body plethysmography, DLCO, 6-min walk test (6MWT), and arterial blood gases analysis. Pulmonary function was investigated with a MasterScreen system (Jaegger, Würzburg, Germany). European Respiratory Society's (ERS) guidelines were followed for all lung function measurements (Miller et al. 2005; Quanjer et al. 1995). Appropriate reference values were applied (Falaschetti et al. 2004; Stocks and Quanjer 1993). DLCO was measured using a single breath-hold method. Following the ATS/ERS 2005 guidelines, the lower limit of normal (LLN) was set at the level of the 5th percentile (or mean −1.645 SD) of each reference population (Pellegrino et al. 2005). The results were expressed as the percent of predicted. However, as the mean predicted value declines with age and the scatter does not decline proportionately, the percent predicted leads to an age-, height-, and sex-related bias. To allay the bias, standardized residuals (SR = (observed − predicted)/residual SD) were calculated (Miller et al. 2011). Data were presented as means and 95 % confidence intervals (CI).

The presence of an obstructive defect was defined as forced expiratory value in 1 s (FEV1)/forced vital capacity (FVC) ratio of less than −1.645 SD and was quantified by the FEV1 expressed in %pred. (mild ≥70 %, moderate 60–69 %, moderate severe 50–59 %, severe 35–49 %, very severe <35 %). A restrictive pattern was defined by a total lung capacity (TLC) less than LLN. The severity of restriction was quantified by TLC expressed in %pred. (mild ≥ 70 %, moderate 60–69 %, severe <60 % pred.). Severity of DLCO defect was graded as mild (>60 %), moderate (40–60 %) and severe (<40 % pred.) (Pellegrino et al. 2005). Respiratory failure was defined as resting hypoxemia with PaO_2 < 60 mmHg with or without hypercapnia ≥45 mmHg at room temperature. 6MWT was administered to evaluate exercise tolerance and oxygen desaturation. A fall in saturation exceeding 4 % was regarded as significant.

2.3 Statistical Analysis

Data were expressed as proportions and means ± SD, or medians with ranges. Chi-squared test, Fisher test, analysis of variance, and non parametric Kruskal-Wallis test were applied for hypothesis testing. A p-value <0.05 was regarded significant.

3 Results

Demographic data and presenting clinical features of the patients with HP are summarized in Table 1. The mean age of the patients was 44.7 ± 12.5 (range 18–67 years). There were 68 women (61.3 %), and 43 (38.7 %) men. During the observation period, 2 patients died awaiting lung transplantation. Seventy five patients (67.6 %) lived in a country farm, having birds or live stock in the vicinity, and 36 patients lived in cities. Exposure to bird antigens was reported by 86 (78.2 %), to both mold and bird antigens by 35 (31.8 %), and molds alone by 48 (43.6 %) patients. Only had 11 (10 %) patients reported no relevant exposure, but presented typical pathological findings on lung biopsy or in BAL. Serum precipitins were present in 68 (61.3 %) patients, mostly to bird proteins (63 patients, 56.8 %). The precipitins were more prevalent with age: 50.0 % of patients <30 years and 73.1 % of patients >70 years of

Table 1 Demographic data and clinical presentation of patients stratified by age at the time of HP diagnosis

Characteristics	Total (*n = 111*) n(%)	<30 years (*n = 14*) n(%)	30–49 years (*n = 45*) n(%)	≥50 years (*n = 52*) n(%)	p-value
Gender					
Men	43(38.7)	5(35.7)	20(44.4)	18(34.6)	0.593[a]
Women	68(61.3)	9(64.3)	25(55.6)	34(65.4)	
Smoking history					
Never	63(56.8)	8(57.1)	25(55.6)	30(57.7)	**0.032**[b]
Ex-smoker	23(20.7)	2(14.3)	5(11.1)	16(30.8)	
Current smoker	25(22.5)	4(28.6)	15(33.3)	6(11.5)	
Duration of symptoms before diagnosis (months; median (range))	12(1–360)	14(3–240)	13(1–360)	12(1–240)	0.851[c]
Symptoms					
Dyspnea	108(97.3)	13(92.9)	45(100)	50(96.2)	0.252[b]
Cough	97(87.4)	11(78.6)	39(86.7)	47(90.4)	0.489[a]
Flu-like syndrome	48(44.0)	5(35.7)	21(47.6)	22(44.0)	0.771[a]
Weight loss	47(54.7)	9(75.0)	16(47.1)	22(55.0)	0.247[a]
BMI < 18.5 (kg/m^2)	4(3.6)	3(21.4)	0(0)	1(1.9)	**0.006**[b]
Signs					
Crackles	83(74.8)	11(78.6)	29(64.4)	43(82.7)	0.112[a]
Digital clubbing	15(13.5)	4(28.6)	7(15.6)	4(7.7)	0.112[a]
Residence					
Country	75(67.6)	9(64.3)	36(80.0)	30(37.7)	0.062[a]
City	36(32.4)	5(35.7)	9(20.0)	22(42.3)	
Exposure	104(94.5)	12(85.7)	45(100)	47(92.2)	0.064[b]
Bird antigen	86(78.2)	10(71.4)	36(89.0)	40(78.4)	0.793[a]
Mold antigen	48(43.6)	428.6)	24(53.3)	20(39.2)	0.181[a]
Precipitins	68(61.3)	7(50.0)	23(51.1)	38(73.1)	0.056[a]
Bird fancier lung	63(56.8)	6(42.9)	21(46.7)	36(69.2)	**0.044**[a]
Farmer's lung	11(10.4)	1(7.1)	3(7.0)	7(14.3)	0.555[b]

[a]Chi-squared test

[b]Fisher's test

[c]Kruskal-Wallis test

age, without borderline statistical significance ($p = 0.056$; Chi-squared test).

The median duration of clinical symptoms before the diagnosis was 12 months (range: 1–360 months). The main symptoms were dyspnea (97.3 %) and cough (87.4 %). Weight loss was reported by 47 (54.7 %) patients and flu-like syndrome by 48 (44.0 %) patients. Body mass index (BMI) was low (<18.5 kg/m^2) in 3.6 % of patients, normal (18.5–25.0 kg/m^2) in 36.0 % of patients, and high (>25 kg/m^2) in 60.4 % of patients. In the patients younger than 30 years of age, BMI <18.5 kg/m^2 was observed in 21.4 % of them; the difference from other groups was significant ($p = 0.006$). Crackles were heard in 83 (74.8 %) patients. Clubbing was observed in 15 (13.5 %) patients. Twenty five patients (22.5 %) were smokers at the time of the diagnosis, 23 (20.7 %) were ex-smokers, and 63 (56.8 %) never smoked. Differences in these groups were statistically significant ($p = 0.032$) (Table 1).

All patients had a high resolution computed tomography (HRCT) performed at the time of diagnosis. 'Active' forms of HP were present in 101 (91.0 %) patients, most commonly in the

group 30–49 years of age (93.3 %) (Table 2). Radiologic signs of fibrosis were present in 48 (43.2 %) patients, equally frequent in the youngest and oldest age-groups. 'Active' changes coexisted with 'chronic' changes in 39 (35.1 %) patients, notably in the youngest age-group. Respiratory insufficiency was present in 27 (24.3 %) patients at the time of diagnosis, with about equal distribution across the age-groups.

The results of pulmonary function tests are summarized in Tables 2 and 3. Of the 111 patients, 109 performed acceptable spirometry test, 105 had whole-body plethysmography, 104 had DLCO test, and 103 performed 6MWT. The most frequent abnormality was reduced DLCO (90.4 %), followed by desaturation during 6MWT (73.8 %). Figure 1b presents DLCO abnormalities in all patients. It was decreased in all the patients of the youngest age-group, in 85.7 % in the middle-aged group, and in 91.8 % of the patients over 50 years of age. Severe DLCO impairment was seen in 69.2 %, 31.0 %, and 18.4 % of patients in respective groups. In turn, moderate and mild DLCO disturbances were observed in 30.8 %, 54.8 %, and 73.5 % of patients in respective groups. The differences in severity of reduced DLCO values were significant between groups ($p = 0.008$; Fisher's test). Normal DLCO was observed only in 9.6 % of all patients (14.3 % in the youngest group and 8.2 % in the oldest group). Significant desaturation in 6MWT was seen in 76 patients (73.8 %), without appreciable inter-group differences. The deepest desaturation was seen in the youngest age-group (median 11 %), as compared with the median of 5 % in the middle-aged group and 6 % in the oldest age-group.

VC was decreased in 46 (43.0 %) and TLC was decreased in 43 (41.0 %) patients. In the less than 30 years of age group VC was decreased in all patients and TLC in 92.3 % of patients. In the middle-aged group VC was decreased in 52.5 % and TLC was decreased in 45.5 % of patients. In the oldest, over 50 years of age group VC was decreased only in 18.4 %, and TLC was decreased in 22.9 % of patients. The differences were significant ($p < 0.001$ for VC and $p < 0.001$ for TLC; Chi-squared test). VC and TLC trends in all patients are plotted out in Fig. 1a, c.

In the youngest age-group, moderate and severe restrictive ventilation disturbances were present in 69.3 % of patients. In the middle-aged group such disturbances were present only in 22.7 % and in the oldest over 50 years of age group in 4.2 % of patients. The inter-group differences were significant ($p < 0.001$; Fisher's test). Airflow obstruction (FEV1/FVC < LLN) was detected in 12 (11.2 %) patients. Six of them never smoked. Using ATS/ERS guidelines to grade the severity (Miller et al. 2005), obstruction was mild in 6 patients, moderate in 4 patients, moderately severe, severe, and very severe in 2 patients each (Table 2).

4 Discussion

HP diagnosis is often challenging and frequently delayed, because symptoms are nonspecific and a relevant history may be absent. Sometimes the diagnosis is supported by clinical improvement upon removal or avoidance of the presumed antigen (Matar et al. 2000). In our cohort, the most frequent subtype of HP was bird fancier's lung (78.2 %). Only did 56.8 % of the patients have bird precipitins in the serum. The remaining subtypes of HP were less common. The prevalence of bird fancier's lung varies widely depending on bird species or bird handling in various countries (Chan et al. 2012).

Long-standing exposure to the offending antigen can result in pulmonary fibrosis. The patients affected typically present with dyspnea, anorexia, weight loss, fatigue, and general malaise (Matar et al. 2000). In our cohort, dyspnea was observed in each age-group with similar frequency: 92.9 % in less than 30 years old, 100 % in 30–49 years old, and 96.2 % in over 50 years old patients. Weight loss and BMI <18.5 kg/m^2 were most prevalent in the youngest patients. It seems a spurious notion that young people spending less time in the countryside or handling pet birds should have a milder form of the disease. Exposure to pet birds at home could likely have a

Table 2 Qualitative character of pulmonary function in hypersensitive pneumonitis patients stratified by age at diagnosis

Functional indices	Total *(n = 111)* n(%)	<30 years *(n = 14)* n(%)	30–49 years *(n = 45)* n(%)	≥50 years *(n = 52)* n(%)	p-value
TLC					
Normal	62(59.0)	1(7.7)	24(54.5)	37(77.1)	<**0.001**[a]
Decreased	43(41.0)	12(92.3)	20(45.5)	11(22.9)	
Normal	62(59.0)	1(7.7)	24(54.5)	37(77.1)	<**0.001**[b]
Mild restriction	22(21.0)	3(23.1)	10(22.7)	9(18.8)	
Moderate restriction	10(9.5)	4(30.8)	4(9.1)	2(4.2)	
Severe restriction	11(10.5)	5(38.5)	6(13.6)	0(0)	
VC					
Normal	61(57.0)	0(0)	21(47.7)	40(81.6)	<**0.001**[a]
Decreased	46(43.0)	14(100)	23(52.5)	9(18.4)	
DLCO					
Normal	10(9.6)	0(0)	6(14.3)	4(8.2)	0.371[b]
Reduction	94(90.4)	13(100)	36(85.7)	45(91.8)	
Normal	10(9.6)	0(0)	6(14.3)	4(8.2)	
Mild + moderate reduction	63(60.6)	4(30.8)	23(54.8)	36(73.5)	**0.008**[b]
Severe reduction	31(29.8)	9(69.2)	13(31.0)	9(18.4)	
6MWT					
Normal	27(26.2)	2(14.3)	12(27.9)	13(28.3)	0.551[a]
Significant desaturation	76(73.8)	12(85.7)	31(72.1)	33(71.7)	
Respiratory insufficiency	27(24.3)	3(21.4)	9(20.0)	15(28.8)	0.577[a]
Obstruction					
No	95(88.8)	13(92.9)	40(90.9)	42(85.7)	0.692[b]
Yes	12(11.2)	1(7.1)	4(9.1)	7(14.3)	
No	95(88.8)	13(92.9)	40(90.9)	42(85.7)	0.599[b]
Mild	6(5.6)	0(0)	3(6.8)	3(6.1)	
Moderate	4(3.7)	0(0)	1(2.3)	3(6.1)	
Moderate, severe, very severe	2(1.9)	1(7.1)	0(0)	1(2.0)	
HRCT					
No changes	1(0.9)	0(0)	1(2.2)	0(0)	0.521[b]
Active changes only	62(55.9)	7(50.0)	29(64.4)	26(50.0)	
Fibrosis only	9(8.1)	1(7.1)	2(4.4)	6(11.5)	
Active changes + fibrosis	39(35.1)	6(42.9)	13(28.9)	20(38.5)	
Treatment	68(61.3)	13(92.9)	27(60.0)	28(53.8)	**0.028**[a]

[a]Chi-squared test

[b]Fisher test

bearing on the severity of disease in young patients. In this study we were unable to assess genetic factors, which could also be at play concerning the course of disease.

In our cohort, chronic form of HP, with a typical HRCT pattern was present in 43.2 %, of patients, with similar frequency in the youngest and oldest age-groups (50.0 %) and less so in the middle-aged group (33.3 %). Imaging findings of

Table 3 Results of pulmonary function tests in hypersensitivity pneumonitis patients stratified by age at diagnosis

		Total	<30 years	30–49 years	≥50 years	
		(n = 111)	*(n = 14)*	*(n = 45)*	*(n = 52)*	p-value*
VC	% pred	80.0 ± 24.1	54.3 ± 17.1	76.7 ± 22.1	89.9 ± 21.5	**<0.001**
	SR	−1.59 ± 2.01	−4.08 ± 1.67	−1.94 ± 1.90	−0.57 ± 1.41	**<0.001**
FEV1/FVC	% pred	80.1 ± 8.8	83.5 ± 7.2	82.4 ± 8.9	77.1 ± 8.2	**0.004**
	SR	−0.04 ± 1.20	0.06 ± 0.98	0.14 ± 1.29	−0.24 ± 1.17	**0.299**
TLC	% pred	87.0 ± 21.4	63.9 ± 12.5	84.9 ± 21.2	95.1 ± 18.6	**<0.001**
	SR	−1.17 ± 1.93	−3.27 ± 1.37	−1.35 ± 1.92	−0.44 ± 1.60	**<0.001**
DLCO	% pred	51.1 ± 18.2	35.8 ± 12.8	54.0 ± 20.5	52.6 ± 15.4	**0.004**
	SR	−3.54 ± 1.47	−5.16 ± 1.17	−3.50 ± 1.63	−3.14 ± 1.05	**<0.001**

Values are means ± SD

SR standardized residual, *FVC* forced vital capacity, *%pred* percent predicted, *FEV1* forced expiratory value in 1 s, *TLC* total lung capacity, *VC* vital capacity, *DLCO* diffusing capacity of the lung for carbon monoxide

*ANOVA

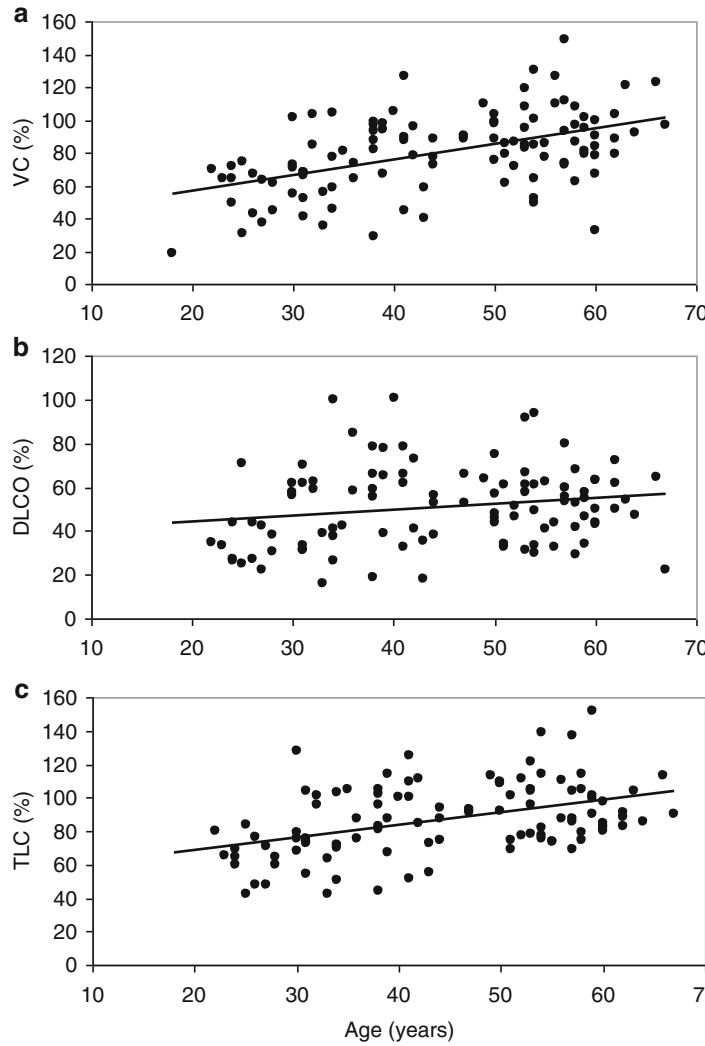

Fig. 1 Plots of (**a**) vital capacity (VC), (**b**) lung diffusing capacity for carbon monoxide (DLCO), and (**c**) total lung capacity (TLC) on age of patients at the time of diagnosis of hypersensitivity pneumonitis

parenchymal fibrosis or pathological pulmonary fibrosis are associated with diminished survival in HP (Lacasse et al. 2012). Abnormalities in pulmonary function are similar in all interstitial lung diseases. However, functional assessment might be helpful in decision making concerning treatment or qualification for lung transplantation. One could presume that older patients would present with a greater defect in pulmonary function, due to smoking, duration of exposure, or residency in the countryside. Contrary to this presumption, we found greater functional abnormalities in the youngest and middle-aged than in the oldest patients. In most HP patients, abnormal lung function is of restrictive pattern, with decreased vital capacity and moderate-to-severe reduction of DLCO (Selman et al. 2012). In our cohort, the restrictive pattern was present only in 41.0 % of patients, mostly belonged to the youngest group, where abnormalities were severe and corresponded with fibrosis. The most frequent functional abnormality also was DLCO impairment, observed in 90.4 % of patients, followed by desaturation in 6MWT that was most prevalent in the youngest group. In this group, DLCO abnormalities were seen in all patients and severe DLCO reduction was present in 69.2 % of patients. In the two older groups, severe DLCO reduction was less frequent. In the oldest group of patients, over 50 years of age, despite fibrosis present in HRCT images, often with massive pleural changes, obstructive functional abnormalities were more common, which may resulted from the smoking habit.

The present findings indicate that the diagnosis of HP in patients less than 30 years of age may signify more severe course of disease, especially in case of bird's breeder disease. This subtype of HP usually runs an insidious course. Together with active fibrosis, this can lead to severe lung function impairment. In older groups, there is probably mixed exposure, causing a milder HP course. It is worth pointing out that during a 1-year follow-up, two young women passed away of respiratory insufficiency and infection, while awaiting lung transplantation. On the other side, none of the older patient passed away, although their lung function has worsened.

Farmers with chronic HP more often develop emphysema, whereas pigeon breeders usually progress to lung fibrosis (Lacasse et al. 2012). In our cohort, emphysema was present only in four patients with bird fancier's lung and all of them had fibrosis. None of them had farmer's lung disease.

5 Conclusions

HP is a complex and difficult to diagnose disease. In the present study we found that young people suffering from HP had more severe clinical symptoms, and also a significant weight loss with low BMI. Radiological signs of lung fibrosis in HRCT images were seen with similar frequency in the youngest, less than 30 years, and the oldest, more than 50 years of age, patients. However, pulmonary function abnormalities, which reflect fibrotic changes, were more severe in the youngest group. That might be caused by the insidiousness of the disease, as it is seen in bird fancier's lung. In older groups, there was probably mixed exposure, causing a milder HP course.

Early diagnosis and antigen avoidance, if only possible, are the key and immediately curative, actions in the management of HP. However, once the disease has caused permanent lung damage, such as fibrosis or emphysema, it is likely to progress even after the elimination of all exposure to the antigen (Lacasse et al. 2012). In the present study we did not focus on the patients' follow-up and treatment outcomes. The current treatment consists of oral or systemic corticosteroids. We opine that the qualification for early lung transplantation should be done, especially in young HP patients with fibrotic disease, regardless of steroid treatment.

Conflicts of Interest The authors declare no conflicts of interests in relation to this article.

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Specific Inhalation Challenge in Persulfate Asthma

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Abstract

Specific inhalation challenge (SIC) may be considered the 'gold standard' for the diagnosis of occupational asthma due to persulfate salts. The aim of the study was to develop a safe SIC protocol. Between 2003 and 2014, eight patients with suspected occupational asthma due to persulfate salts were examined (7 females, all hair-dressers). SIC was done with a dosimeter and a nebulizer using ammonium persulfate dissolved in phosphate buffer. Until 2009, a four-step-protocol (doses: 0.0004, 0.0045, 0.045, 0.45 mg; cumulative: 0.5 mg) was used, afterwards a six-step-protocol (doses: 0.0004, 0.0018, 0.007, 0.028, 0.113, 0.45 mg; cumulative: 0.6 mg). With each SIC protocol, four subjects were tested. Skin prick tests with ammonium persulfate (20 mg/mL) were performed in all and patch tests in four subjects. In total, four subjects showed a positive SIC, two with each protocol. All subjects showed an isolated late reaction. The greatest decrease of volume in 1 s was 35 % about 3.5 h after the last inhalation (four-step-protocol). Skin prick test with ammonium persulfate was positive in one SIC positive (2 mm wheal) and in two SIC negative patients (3 and 4 mm wheal). All four subjects tested with patch tests showed a positive reaction; three of them were SIC_{pos}. We recommend to include patch-testing in the diagnosis of suspected occupational asthma due to persulfate salts. Isolated late asthmatic reactions may occur after SIC. The proposed six-step SIC protocol was safe in this limited number of subjects.

Keywords

Hairdressers • Occupational asthma • Occupational disease • Patch test • Skin prick test

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1 Introduction

Persulfate salts are low-molecular-weight allergens and may induce rhino-conjunctivitis, asthma, contact urticarial, and anaphylaxis (Hoekstra et al. 2012; Hougaard et al. 2012). Predominantly hairdressers are exposed to persulfate salts during hair bleaching (Moscato et al. 2005; Merget et al. 1994), but epidemiological data of allergic diseases due to persulfate are rare. From 2007 to 2012 at least 148 patch tests with ammonium persulfate were found positive (18.7 %) in 696 hairdressers with suspected contact dermatitis in Germany (Uter et al. 2014).

So far the pathogenesis and the value of diagnostic tests (e.g., skin prick test) in persulfate asthma are still unclear. Therefore specific inhalation challenges (SICs) are considered the 'gold standard' in the diagnosis of persulfate asthma. Standardized SICs with persulfate have been described previously. Munoz et al. (2003, 2004) used potassium persulfate powder in increasing concentrations (5, 10, 15, and 30 g mixed in 150 g lactose) and the tested subject had to tip powder from one tray to another. Moscato et al. (2005) nebulized ammonium persulfate dissolved in distilled water (mean concentration: 1.01 ± 0.11 mg/μL) and performed a one-step SIC lasting 30 min.

Since 2003, eight patients with suspected occupational asthma due to persulfate were examined in our outpatient clinic. All of the patients underwent a SIC with one of two newly developed very similar protocols.

2 Methods

The Ethics Committee of the Ruhr-University Bochum gave approval to perform the study. All patients transferred to our outpatient clinic with suspected occupational asthma due to persulfate between 2003 and 2014 were included in this retrospective analysis (Patient 3 had been presented by Harth et al. (2006), Polychronakis et al. (2013) presented patient 6). All patients answered a questionnaire for medical history and underwent a physical examination, laboratory routine parameters including blood cell count, total immunoglobulin E (IgE), electrocardiogram, exhaled nitric oxide (eNO; Niox Mino, Aerocrine, Solna, Sweden), and X-ray of the thorax.

Lung function measurements (spirometry and body plethysmography; Carefusion, Würzburg, Germany) were performed according to the guidelines of the American Thoracic Society (ATS). The European Community for Steel and Coal (ECSC) reference values for spirometry were chosen (Quanjer et al. 1993). Methacholine testing was performed with a reservoir method as described by Polychronakis et al. (2013). Bronchial hyperresponsiveness was assumed if (i) forced expiratory volume in 1 s (FEV_1) was reduced ≥20 % or (ii) specific airway resistance (sRt) doubled and increased to ≥2.0 kPa/s with a cumulative dose of ≤300 μg methacholine. Sputum induction with 0.9 % saline and processing of sputum samples were done as described by Raulf-Heimsoth et al. (2011). Skin prick tests were performed in all subjects with 20 environmental allergens and with ammonium persulfate (20 mg/mL, Sigma-Aldrich, Seelze, Germany). A wheel diameter of at least 2 mm was defined as positive. Patch testing was performed with 2.5 % ammonium persulfate (HAL; Düsseldorf, Germany) in four subjects. The patch remained on the back for 24 h, reactions were read at 24, 48, and 72 h.

SIC was carried out on 1 day with an APSpro dosimeter (Carefusion, Würzburg, Germany) combined with a 646 DeVilbiss nebulizer. Ammonium persulfate was freshly dissolved in phosphate buffer for all tests. Until 2009 (subjects 1–4), a four-step protocol was used. Each dose of ammonium persulfate was administered by inhalation of five slow deep breaths from functional residual capacity to near total lung capacity. During each breath the nebulizer acted for 0.6 s with an output of about 900 mg/min and an inspiratory airflow of about 1 L/s. Tenfold concentrations of 0.01, 0.10, 1.00, and 10.00 mg ammonium persulfate per mL were used resulting in doses that increased from 0.40 μg to 0.45 mg, with a cumulative dose of 0.50 mg (SIC protocol I).

Table 1 Personal data of 8 patients with suspected occupational asthma due to ammonium persulfate

	Four-step-protocol				Six-step-protocol			
	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6	Pat 7	Pat 8
Gender	f	f	f	f	f	m	f	f
Age (years)	44	30	27	24	39	32	20	46
Atopy	no	yes	yes	yes	no	yes	yes	yes
Smoking	yes	yes	yes	yes	yes	yes	never	never
Exposure time (months)	288	60	108	84	264	15	36	284
Latency period[a] (months)	240	2	96	24	216	0	24	12
Exposure time with symptoms (months)	48	58	1	60	48	15	6	48
Time between end of exposure and examination (months)	12	14	7	7	7	6	12	8
Asthma medication	yes	yes	yes	yes	no	yes	yes	yes

PAT patient

[a]Time between starting exposure and development of symptoms

Since 2010, a six-step-one-day SIC with quadrupling doses (SIC protocol II) was used (subjects 5–8). The inhalation procedure was the same as in protocol I, but ammonium persulfate concentrations were applied in quadrupling concentrations (0.010, 0.039, 0.156, 0.625, 2.500, and 10.000 mg/mL), doses increased from 0.40 μg to 0.45 mg, with a cumulative dose of 0.60 mg.

According to both SIC protocols, after inhalation of saline patients inhaled the ammonium persulfate solution with time-lags of 10 min. Lung function was measured before SIC, after each inhalation step, 30, 60, and 120 min and about 24 h after SIC. The measurements of bronchial hyperresponsiveness, eNO, and sputum analysis were performed before and about 24 h after SIC. Anti-obstructive medication was withheld at least 24 h before SIC.

As positivity criteria of SIC we used the same lung function changes from baseline as for methacholine testing after any ammonium persulfate dose. A late reaction was defined as a positive reaction beginning later than 2 h after the end of exposure.

3 Results

Eight patients (7 women, 1 man) with suspected occupational asthma due to persulfate were examined between 2003 and 2014. While all women were hairdressers, the male subject was a chemical worker. One woman had been examined in another hospital previously (patient 1). The age of the patients ranged from 20 to 46 years. Six patients showed atopy in skin prick tests and only two were never-smokers (Table 1).

Three patients showed a positive SIC, two of them with the four-step protocol. Patient 5, who underwent a six-step SIC, showed a FEV_1 decrease of 18 % 2 h after the last inhalation step and was defined positive, too (overall 4 positive SICs). In all cases, the reaction was a late one (Fig. 1a). Patient 1 was diagnosed with occupational asthma due to persulfate 19 months earlier in another hospital, where she underwent a SIC with persulfate and showed a positive reaction. This positive reaction could not be reproduced with our test (overall 4 negative SICs).

The latency period (time between starting exposure and first symptoms) in SIC positive women (including patient 1) was 2 to 240 months and in SIC negative 12 to 24 months. Total exposure time was 60 to 264 months in SIC positive women and 16 to 84 months in SIC negatives. The only man (SIC positive) was exposed for 15 months and his symptoms appeared shortly after he had started to work. At the time of examination all but one patient took antiobstructive medication (Table 1). Work-related symptoms of the nose and skin were

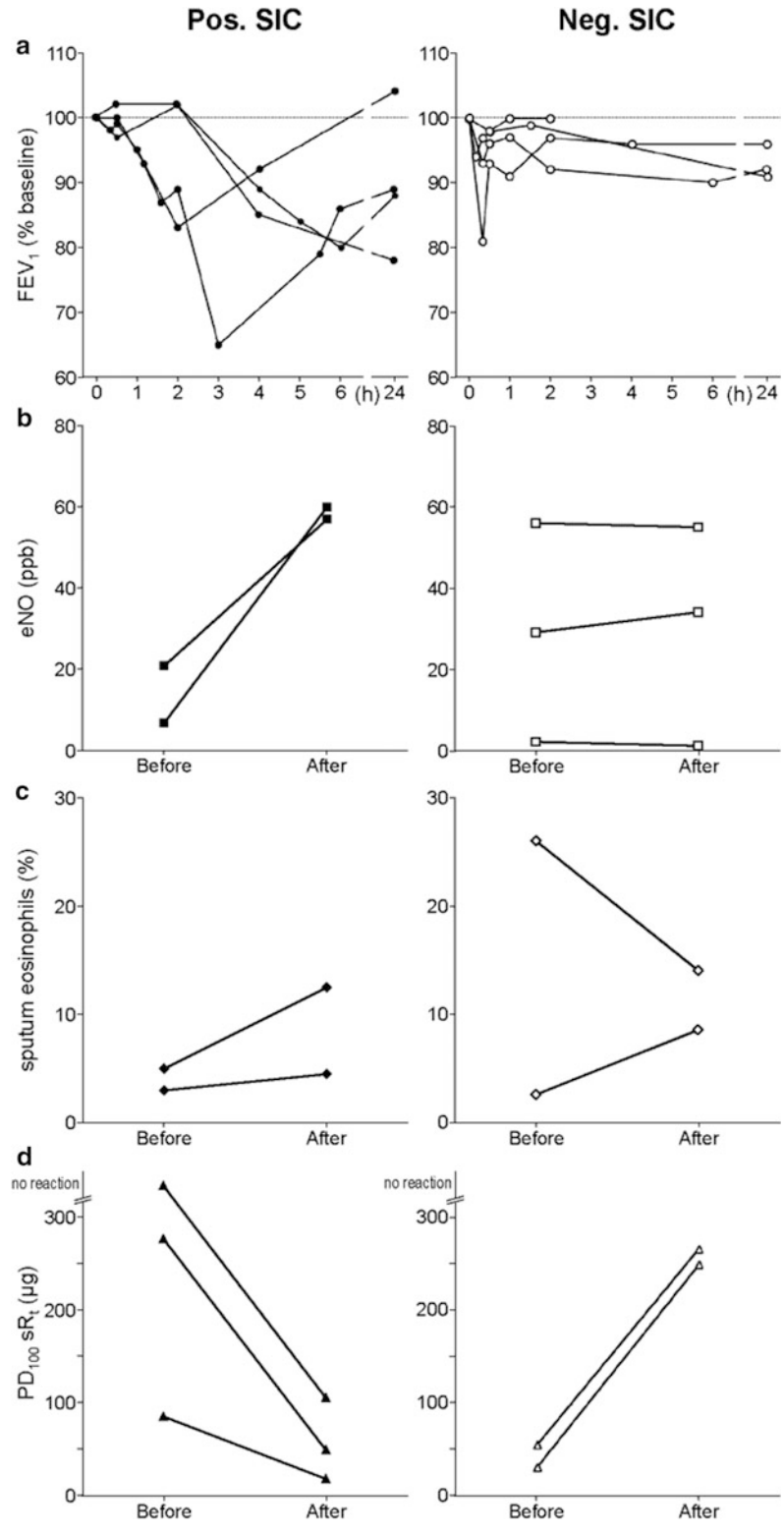

Fig. 1 (**a**) **Time-response curve of FEV_1 during specific inhalation challenge (SIC)**. The near-positive immediate type reaction was considered negative due to insufficient breathing technique and lack of symptoms and change of specific airway resistance. (**b**) Serial measurements of eNO; (**c**) sputum eosinophils; and (**d**) methacholine responsiveness all performed before and 24 h after SIC

Table 2 Work-related symptoms and diagnostic findings

	Four-step-protocol				Six-step-protocol			
	Pat 1[a]	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6	Pat 7	Pat 8
Symptoms								
Skin	yes	yes	no	no	yes	yes	no	yes
Eyes	no	no	no	no	no	no	no	no
Nose	yes	yes	yes	yes	yes	yes	no	yes
Cough	yes	no	no	no	no	no	yes	yes
Phlegm	yes	no	no	no	no	no	no	no
Dyspnea	no	yes	yes	yes	yes	yes	yes	yes
Diagnostic findings								
FEV_1 (%pred.)	84	91	100	100	108	89	106	90
Methacholine challenge								
$PD_{100}sR_t$	55	41	278	neg.	neg.	62	neg.	52
$PD_{20}FEV_1$	162	48	215	104	neg.	153	neg.	56
Sputum eosinophils (%)	0	5	10	3	2	6	1	7
Total IgE (kU/L)	172	575	133	273	228	702	127	40
SPT with APS (wheal and flare, mm)	neg.	2 (10)	neg.	neg.	neg.	neg.	4 (10)	3 (3)
Patch test with APS	n.d.	n.d.	pos.	n.d.	pos.	pos.	n.d.	pos.
SIC with APS	neg.	late	late	neg.	late	late	neg.	neg.

PAT patient, $PD_{20}FEV_1$ a 20 % fall in forced expiratory volume in 1 s (FEV1), $PD_{100}sRt$ doubling of specific airway resistance, *SPT* skin prick test, *APS* ammonium persulfate, *SIC* specific inhalative challenge, n.d. not done
[a]Diagnosis of occupational asthma due to APS was based on SIC outcome in another clinic some months before

frequent (Table 2). Lung function testing was normal in all patients, but only two SIC negative patients did not show bronchial hyperresponsiveness.

Total IgE concentrations were elevated in all but one SIC negative patients (normal: <100 kU/L) (Table 2). Blood eosinophils were increased to ≥5 % in all but two SIC negative patients (data not shown). Skin prick test with ammonium persulfate was positive in one SIC positive and in two SIC negative atopic women. Patch tests were performed in four patients, all with a positive reaction. Three of them were SIC positive. SIC was performed in each patient (Fig. 1). During SIC, two patients (no. 2 and no. 3) reported runny nose. All positive tests were late bronchial reactions. The highest decrease of FEV_1 of 35 % was seen about 3.5 h after the end of exposure. Three patients were given antiobstructive medication (patients 3, 6, both SIC positive; patient 8, SIC negative).

Serial measurements of eNO were performed in 5 patients (Fig. 1b). In two SIC positive, but in no SIC negative patient, there was a significant increase in eNO after SIC. Eosinophils in induced sputum were analyzed in four subjects. In three cases there was an increase in eosinophils (including one SIC negative patient) (Fig. 1c). Bronchial hyperresponsiveness increased in three of the four patients (one was not examined). In SIC negative patients there was an increase of bronchial reactivity (Fig. 1d).

4 Discussion

SICs are generally considered as the 'gold standard' in the diagnosis of occupational asthma. This is especially true for persulfate allergy because there is no *in vitro* test available for the demonstration of sensitization (Hougard et al. 2012; Moscato et al. 2005). Symptoms at work cannot predict the existence of occupational asthma either (Moscato et al. 2005; Blainey et al. 1986).

Munoz et al. (2003, 2004) and Moscato et al. (2005) have previously performed semi-quantitative SICs with persulfate, but they exposed their patients to unknown, probably high concentrations. To our knowledge, so far no quantitative test protocols allowing the calculation of the dose required for a positive reaction have been published. This would be important for both immediate and isolated late reactions in order to avoid too low or unnecessarily high maximal doses, with the risk of false positive or severe asthmatic reactions. We herein present a multiple-step, one day SIC protocol to diagnose occupational asthma due to ammonium persulfate with increasing exposure concentrations from 0.01 to 10 mg/mL and cumulative doses of 0.5 or 0.6 mg, respectively.

Skin prick test with persulfate, mostly performed with ammonium persulfate, may show immediate type reactions (Munoz et al. 2003, 2004, 2008; Wrbitzky et al. 1995; Parra et al. 1992), but in most cases late reactions are induced. Moscato et al. (2005) noted 14 isolated late reactions in 21 SIC positive patients and Munoz et al. (2004) 6 late reactions in 8 positive SICs. Also Blainey et al. (1986) saw only late reactions ($n = 15$). This is in accordance with our present results.

In the present study, one patient showed a decrease of FEV_1 of about 35 % (patient no. 3) while in the other cases the decrease was smaller. In the study of Munoz et al. (2003), patients handled a mixture of 150 g lactose and 5 g potassium persulfate powder and the measured air levels of total dust ranged from 1 to 6 mg/m^3. In 5 of 8 positive SICs, a fall of FEV_1 of about 30–40 % was induced. Moscato et al. (2005) nebulized persulfate solution in a concentration of about 1.01 ± 0.11 mg/μL. In their study the maximum decrease of FEV_1 was also about 40 % (three patients). We assume that the presented six-step SIC protocol is less aggressive and ensures a higher security to the patients to prevent excessive FEV_1 decreases.

The early four-step protocol with ten-fold dilutions was replaced by a six-step protocol with quadrupling doses due to safety reasons. Although the lowest and highest single doses were identical in both protocols, the cumulative dose was marginally higher in the six-step protocol. Overall, the observed degrees of airways obstruction were considered acceptable. Due to the limited number of tests, further studies will be required in order to estimate whether the proposed protocol indeed will be sufficiently safe.

In four patients of the present study, SIC was negative. Patient no. 1 had shown a positive SIC reaction some months ago in a previous external examination and was therefore diagnosed as occupational asthma due to persulfate. We do not know any details of this test which was performed by a 15-min handling of bleaching powder. It is possible that the patient became negative in our examination due to the time lapse from the external SIC. Improvement of occupational asthma due to persulfate after avoiding exposure was described in literature (Munoz et al. 2008). Patient no. 8 was sensitized to ammonium persulfate and showed bronchial hyperresponsiveness, but had a negative SIC.

Concerning the sensitivity of our SIC protocols, we cannot exclude false negative reactions, but in view of the high maximal fall in FEV_1, the increase of the maximal dose should be performed cautiously, possibly a 2-day protocol should be considered. We have not performed SICs with ammonium persulfate in controls, but the negative SICs in patients with bronchial hyperresponsiveness and the lack of an immediate reaction indicate high specificity. An association was seen between a positive patch test and a positive SIC. On the other hand, there were no associations between the results of SIC and smoking, atopy, or skin prick test with ammonium persulfate. This is in accordance with other studies (Moscato et al. 2005). As a result of our findings we recommend to include patch testing in the diagnostic procedure, which has rarely been reported in the literature.

We also tested parameters indicating airways inflammation before and after SIC. The interpretation of the results of these tests (serial testing of eNO, sputum eosinophils, and bronchial hyperresponsiveness) is limited by a considerable number of missing values. However, there was an overall concordance between

eosinophilic airway inflammation and SIC results. We consider these additional effect parameters especially useful for the detection of isolated late reactions which are sometimes difficult to document. These tests also indicate that isolated late reactions may be mediated by eosinophilic inflammatory processes.

Conflicts of Interests The authors declare no conflict of interest in relation to this article.

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Inflammatory Activity in Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is a severe neurodevelopmental disorder in early childhood characterized by impairment in communication and behavior. Recent research is focused on the immune dysregulation as a potential pathomechanism leading to ASD. Thus, we addressed the hypothesis that inflammatory activity might be enhanced in children suffering from ASD. We examined 15 children with ASD (13 boys/2 girls, mean age of 9.3 ± 0.7 years) and 20 age/gender-matched healthy subjects as a control group. All children were medication free and in good health. Hematological parameters in venous blood and plasma levels of pro-inflammatory cytokines - tumor necrosis factor alpha (TNF-α), interleukin 1ß (IL-1ß), and interleukin 8 (IL-8) – were assessed in each subject using human ultra-sensitive ELISA kits. In addition, TBARS as a marker of oxidative stress was evaluated. We found that the level of IL-8 was significantly increased in the ASD children, whereas the other markers remained unappreciably changed compared to controls ($p = 0.003$). In conclusion, the study demonstrates a discrete immune dysfunction in ASD of pro-inflammatory character.

Keywords

Autism • Childhood • Cytokines • Immune dysfunction • Neurodevelopment

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1 Introduction

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders characterized by severe impairments in social interaction and communication, and restricted stereotyped behavior that manifests in early childhood (American Psychiatric Association

2013). The etiology and pathogenesis of ASD are unknown and likely involve complex interactions between genetic, epigenetic, and environmental factors.

Recent studies have emphasized the interaction between genes that encode immune-related proteins and ASD, suggesting a long-term impact of abnormalities of the neuroimmune system on brain development and synaptic functions (Depino 2013; Enstrom et al. 2009). Deverman and Patterson (2009) have reported that cytokines are at play in the neurodevelopment, including progenitor cell differentiation, cellular localization/migration in the nervous system, and synaptic network formation. Blockade of interleukin-1ß (IL-1ß) results in a reversible impairment of long-term potentiation and can alter synaptic plasticity, and this cytokine is also critical in embryonic neurodevelopment (Schneider et al. 1998). Likewise, tumor necrosis factor alpha (TNF-α) is thought to play an important role in synaptic pruning (Cacci et al. 2005). Moreover, emerging evidence implicates cytokines in higher neurological functions, including cognition and memory (Derecki et al. 2010; Bernardino et al. 2008). Thus, abnormal inflammatory activity could contribute to behavioral and neurological dysfunction in ASD (Goines and Ashwood 2013; Ashwood et al. 2011a).

Several studies have shown immune dysfunction in ASD patients such as an abnormal T helper cell profile (Ashwood and Wakefield 2006) or increased level of complement (Corbett et al. 2007). With regard to cytokines, higher plasma levels of the pro-inflammatory interleukins IL-1β, IL-6, and IL-12p40 (Ashwood et al. 2011a), and, conversely, decreased levels of the anti-inflammatory transforming growth factor (TGF-β) have been reported in ASD (Ashwood et al. 2008). Moreover, poor communication and impaired social interaction seems associated with elevated levels of cytokines (Ashwood et al. 2011a, b). Notwithstanding the possible influence of cytokines on the core defects of ASD, the characterization of cytokine profile in this disorder is far from being complete. Therefore, the aim of this study was to investigate the inflammatory activity, as assessed from the plasma cytokine levels, in children suffering from ASD.

2 Methods

2.1 Subjects

The study was approved by the Ethics Committee of Jessenius Faculty of Medicine in Martin, Slovakia and was conducted in accord with the Helsinki Declaration of the World Medical Association. All children/patients/guardians were carefully instructed about the study protocol and they gave informed written consent to participate in the study.

We examined 15 children (13 boys/2 girls) diagnosed with ASD of the mean age of 9.3 ± 0.7 years and 20 age- and gender-matched healthy children (9.6 ± 0.8 years). The ASD diagnosis was ascertained by two independent specialists - child and adolescent psychiatrists according to Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association 2013). After this initial procedure, the diagnosis of ASD, no-regression form, and absence of any symptoms of other psychiatric diagnoses were confirmed by supervising qualified specialist in child and adolescent psychiatry prior to inclusion in this study. Additionally, only the patients who have never received any treatment prior to the study were included in this study.

The control group was recruited from healthy normally developing children of primary school with respect to age and gender and they did not take any medication. Furthermore, the control participants were free of any mental disorders. The following exclusion criteria were used for both groups (ASD patients and controls): no evidence of acute respiratory or infectious disease, no history of cardiovascular, endocrinological, neurological, or other disorders/factors known to affect inflammatory indices in the plasma.

2.2 Blood Analysis

Peripheral blood was collected from each subject into EDTA test-tubes after fasting. Basic hematological parameters were evaluated using a hematology analyzer (Mindray BC-5500, China). Then, the blood was centrifuged for 15 min, and the plasma kept frozen at −80 °C until assayed for cytokine plasma concentrations. The plasma levels of interleukin-1ß (IL-1β), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) were quantified using human ultrasensitive ELISA kits (Invitrogen, Carlsbad, CA), with the sensitivity level of 0.4–25 pg/mL. The absorbance was measured spectrophotometrically at 450 nm with a PR 2100 microplate reader (Bio-Rad, Dynex, Hemel Hempstead, UK) and calculated in pg/mL from the standard curve using ReaderFit (Hitachi Solutions America, San Bruno, CA). In addition, the thiobarbituric acid-reactive substances (TBARS), indicating lipid peroxidation as a marker of oxidative stress, were analyzed in the plasma using OxiSelect™ TBARS Assay Kit (Cell Biolabs; San Diego, CA). All experiments were performed and tested in duplicate.

2.3 Statistical Analysis

Data were expressed as means ± SE. The Mann-Whitney U test was used for inter-group comparisons of non-Gaussian distributed data and an unpaired t-test for Gaussian distributed data. A p-value of $p < 0.05$ was considered as indicative of significant differences. Statistical elaboration was performed with a commercial software package Systat 10 for Windows (SSI, Richmond, CA).

3 Results

3.1 Hematological Indices

The absolute and percentage values of monocytes were significantly increased ($p = 0.003$) and there was a tendency toward a higher count of white blood cells ($p = 0.07$) in the ASD group compared to controls. No significant differences were found in other parameters (Table 1).

3.2 Cytokine Profile and Oxidative Stress Assay

The plasma level of IL-8 was significantly higher in children with ASD compared to controls ($p = 0.003$, Fig. 1). There were no significant differences in the other proinflammatory markers IL-1ß and TNF-α or in TBARS between the ASD and control groups.

4 Discussion

Despite the fact that the etiology and pathogenesis of ASD are still unclear, it is suggested that there may be an association with immune dysfunction (Onore et al. 2012; Ashwood et al. 2011a). Cytokines are proteins that control the intensity, duration, and type of immune response. However, cytokines are also involved in brain development and synaptic functions including processes of differentiation, migration, proliferation, and behavioral impairments (Onore et al. 2012; Ashwood et al. 2011a). For example, neuropoietic cytokines, such as IL-6, can directly alter cortical neuron dendrite development, neural activity, long-term potentiation, and neurodevelopment, which all may influence behavior (Ashwood et al. 2011a, b; Gilmore et al. 2005). Similarly, IL-1β nad TNF-α have been linked with neurite growth and the regulation of synaptic plasticity in the hippocampus (Cacci et al. 2008). Therefore, the abnormalities in the cytokine profile could represent an important potential pathomechanism leading to impaired neuronal development in ASD (Ashwood et al. 2011a).

In the present study, we found a higher number of monocytes and increased plasma concentrations of IL-8, which indicates abnormal inflammatory activity in children with ASD.

Table 1 Basic hematological indices in autism spectrum disorders (ASD) and controls

	Controls	ASD	P-value
WBC (10^9/L)	6.91 ± 0.42	7.96 ± 0.37	0.070
Neu [10^9/L (%)]	3.38 ± 0.34 (47.4 ± 1.8 %)	3.91 ± 0.36 (48.1 ± 3.2 %)	0.117
Lym [10^9/L (%)]	2.75 ± 0.12 (41.2 ± 1.8 %)	3.07 ± 0.26 (39.2 ± 3.2 %)	0.283
Mon [10^9/L (%)]	0.49 ± 0.03 (7.2 ± 0.4 %)	0.67 ± 0.04 (8.5 ± 0.6 %)	0.003
Eos [10^9/L (%)]	0.27 ± 0.04 (3.9 ± 0.4 %)	0.29 ± 0.04 (3.8 ± 0.5 %)	0.453
Bas [10^9/L (%)]	0.03 ± 0.01 (0.4 ± 0.04 %)	0.03 ± 0.003 (0.4 ± 0.04 %)	0.592
RBC (10^{12}/L)	5.04 ± 0.08	5.21 ± 0.20	0.777
HGB (g/L)	143.6 ± 2.5	143.4 ± 5.6	0.350
HCT (%)	43.0 ± 0.7	43.6 ± 1.8	0.484
MCV (fL)	85.5 ± 1.0	83.7 ± 1.4	0.315
MCH (pg)	28.5 ± 0.3	27.6 ± 0.4	0.091
MCHC (g/L)	333.6 ± 1.6	329.5 ± 2.2	0.153
RDW-CV (%)	12.0 ± 0.1	12.3 ± 0.1	0.153
RDW-SD (fL)	41.5 ± 0.6	41.2 ± 0.7	0.702
PLT (10^9/L)	290.1 ± 12.6	281.9 ± 17.4	0.708
MPV (fL)	8.8 ± 0.2	8.5 ± 0.3	0.504
PDW	16.3 ± 0.1	16.3 ± 0.1	0.828
PCT (%)	0.26 ± 0.01	0.24 ± 0.01	0.330

Data are means ± SE

WBC white blood cells, *Neu* neutrophils, *Lym* lymphocytes, *Mon* monocytes, *Eos* eosinophils, *Bas* basophils, *RBC* red blood cells, *HGB* hemoglobin, *HCT* hematocrit, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *RDW-CV* red blood cell distribution width – coefficient of variation, *RDW-SD* red blood cell distribution width – standard deviation, *PLT* platelets, *MPV* mean platelet volume, *PDW* platelet distribution width, *PCT* plateletcrit

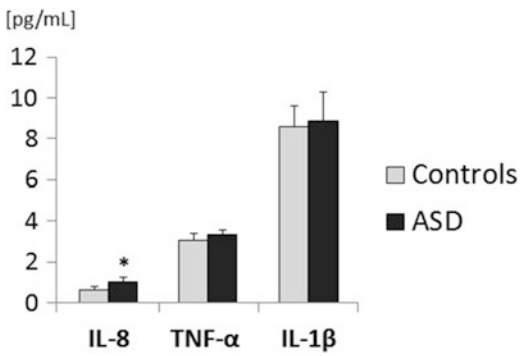

Fig. 1 Cytokine profile in autism spectrum disorders (ASD) and controls. *IL-8* interleukin 8, *TNF-α* tumor necrosis factor alpha, *IL-1β* interleukin 1ß. Data are means ± SE, *p < 0.01

These results are in agreement with other findings which have reported increases of a number of cytokines, including IL-8, in plasma of these children (Ashwood et al. 2011a). Notably, the finding of increased plasma IL-8, a chemoattractant cytokine of important role in the inflammatory process, corresponds to IL-8 increases seen in the brain and cerebrospinal fluid in ASD (Vargas et al. 2005). Higher plasma levels of other chemokines, such as MCP-1 or eotaxin, have also been found in ASD (Ashwood et al. 2011b), although in the present study we did not observe increases in IL-1β or TNF-α, Thus, it seems that IL-8 is the most sensitive pro-inflammatory factor in ASD children. However, the reason why this chemokine is selectively increased in ASD is currently unclear. Generally, chemokines produced by macrophages and other cell types, such as epithelial and endothelial cells, have chemotactic activity toward neutrophils and play important roles in the innate immune response. It is assumed that the elevation of IL-8 in the peripheral circulation indicates the activation of innate immunity. However, higher IL-8 plasma levels may also result from IL-17 secretion by Th17 cells

activated in response to subclinical infections in epithelial or endothelial cells in ASD (Suzuki et al. 2011). Furthermore, IL-8 is associated with impaired stereotypical behavior, and negatively correlates with cognitive and adaptive ability, and with receptive and expressive language (Ashwood et al. 2011a). It seems that the question of whether the enhancement of IL-8 is a result of abnormal immune response in children with ASD or is only a reflection of the chronic autism-related symptoms remains unresolved. In this context, it is currently questionable whether the plasma increase of IL-8 has a pathogenetic role in autism, and whether anti-IL-8 therapy could be useful.

In the present study we did not confirm the presence of higher IL-1β and TNF-α in the plasma of ASD children, reported by others (Suzuki et al. 2011), which could be explained by potentially inhibitory effects exerted by other inflammatory markers. A study of Tilg et al. (1994) has referred to an inhibitory influence of IL-6 on the synthesis of IL-1ß and TNF-α. The IL-8 and IL-6 cytokines also are induced by activation of the nuclear factor-kB, a critical factor in inflammation and apoptosis, which is increased in peripheral blood mononuclear cells in ASD (Noriega and Savelkoul 2014). Therefore, we might speculate that increased IL-8 observed in the present study might also inhibit IL-1ß and TNF-α synthesis, the way IL-6 does. The enhancement of cytokines in ASD may also depend on the type of disorder. A recent study has reported that cytokines are predominantly higher in children with a regressive form of ASD than in those with no regression (Ashwood et al. 2011a). The present study included only children with no regressive type of ASD, which may explain divergent findings on ASD-linked abnormal inflammatory activity.

The mechanisms underlying immune dysfunction in ASD are still debatable. The persistent pro-inflammatory status observed in ASD might be of genetic background. For example, polymorphism in the gene encoding tyrosine kinase receptor MET increases the risk of autism and is a negative regulator of immune response (Enstrom et al. 2010). Alternatively, immune alterations could represent a long-term maladaptation to early events, which could be mediated by epigenetic modifications of cytokine promoters, altered receptor signaling, or other unknown mechanisms. Evidence from laboratory animals shows that early peripheral or maternal immune activation can lead to long-term alterations in immune response (Depino 2013; Williams et al. 2011). That also could represent a potential pathomechanism leading to developmental trajectory of immune dysfunction associated with ASD.

Further, cytokines represent a common language between immune and nervous systems (Goines and Ashwood 2013). Specifically, the vagal system plays an essential role in the bidirectional relationship between the brain and the immune system *via* cholinergic anti-inflammatory pathway, i.e., "inflammatory reflex" (Tracey 2002). Decreased vagal function is associated with increased pro-inflammatory markers and acute-phase proteins indicating poor health. In this context, it is worth noting that recent studies demonstrate reduced vagal activity, as expressed by lower heart rate variability, in ASD patients (Porges et al. 2013). Taken together, we surmize that altered inflammatory reflex could contribute to impairment of immune-neural interaction resulting in discrete regulatory abnormalities associated with autism spectrum disorders.

5 Conclusions

Cytokines are necessary for normal neurodevelopment and behavior and any perturbation in the cytokine network influences functional brain maturation. In this context, the present findings of elevated plasma concentrations of cytokines, in particular IL-8, could reflect dysfunctional neuroimmune mechanisms in ASD. The characterization of inflammatory activity in ASD has implications for the diagnosis and understanding of the pathomechanism leading to autism spectrum disorders.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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How Do Skeletal Muscles Die? An Overview

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Abstract

Clarifying the confusion regarding the term "muscle death" is of great importance, especially for clinicians. In response to various stimuli, skeletal muscle may undergo pathological changes, leading to muscle atrophy and consequently resulting in the loss of muscle strength and function. Depending on the stimulus, skeletal muscles can be induced to die through different mechanisms mainly via apoptosis, autophagy and necrosis. Muscle death may occur secondary to various physiological and pathological conditions such as aging, starvation, immobilization, denervation, inflammation, muscle diseases and cancer. This overview aims to elucidate the medical terminology and pathways used to describe muscle death, which are commonly confused. In addition, some of the common pathological conditions that lead to muscle death such as cachexia and sarcopenia of aging are dwelled on.

Keywords

Apoptosis • Autophagy • Cachexia • Cell death • Muscle atrophy • Necrosis • Sarcopenia • Skeletal muscle

1 Introduction

Skeletal muscle is the largest tissue in the human body, accounts for approximately 40 % of its total mass. As the main reservoir of amino acids in the body, skeletal muscle tissue is subjected to cycles of atrophy and hypertrophy in response to different stimuli such as starvation, physical activity, developmental processes and myopathies (Schwartz 2008). Skeletal muscle cells are post-mitotic cells that arise during embryogenesis from precursor cells known as

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myoblasts. Once skeletal muscle cells are formed during the initial stages of embryogenesis, they never reproduce again. Therefore, the number of skeletal muscle cells is fixed after birth and when the cell dies, it will not be replaced. However, individual muscle cells can grow by increasing their diameter and the number of muscle fibers they contain (Dubinska-Magiera et al. 2013).

The way skeletal muscle 'choose' to die is not always simple to understand (Brooks and Myburgh 2014). There are three main ways of muscle death: (1) apoptosis and paraptosis which are programed cell death, (2) necrosis, and (3) autophagy. Although they all lead to myofiber death, their pathways are somewhat different. Apoptosis often begins due to activated response to signals resulting from DNA damage or loss of cell-survival factors. Its main pathway is anti-apoptotic proteins (e.g., Bcl-X_L). The main pathway of paraptosis is kinase RIP1 (RIPK1). Necrosis is associated with inflammation and phagocytosis and is characterized by damage to myofiber. The autophagic process in skeletal muscle is a non-selective degradation pathway that is mostly related to macroautophagy, but a few are associated with chaperone-mediated autophagy and microautophagy.

Various physiological and pathological conditions can adversely affect the vitality and quality of muscle fibers. Thus, there may be 'more than one way to the end'. Many conditions can lead to muscle death, including disuse, inactivity, or immobilization. Other conditions may be sarcopenia, the age-related loss of muscle mass and strength, some primary muscle diseases, such as the Duchenne disease which lead to muscular dystrophy, and other pathologies, such as cancer which lead to cachexia. Another condition is intensive-care-unit-acquired muscle weakness, with a 30 % incidence among respiratory patients (Yosef-Brauner et al. 2015). Each one of these conditions is associated with certain underlying mechanisms such as inflammation mediated by increased levels of pro-inflammatory cytokines, nuclear factor kappa-B (NF-κB), or oxidative stress characterized by imbalance between free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), and antioxidant agents such as superoxide dismutase, catalase, glutathione, and vitamins C, A, and E. Other mechanisms of muscle death include increased degradation of contractile proteins (e.g., actin, myosin, titin, and troponin) and non-contractile muscle proteins (e.g., cytoskeleton fibers), decreased rate of muscle protein synthesis, dysfunction of enzymes, such as matrix metalloproteinases type 2, 9, and 13, changes in the basement membrane that interfere with channels and receptors function, and decreased activity of enzymes involved with bioenergetic systems, such as creatine phosphokinase (CPK) and ATPase (Brand et al. 2013). Typical markers of skeletal muscle damage include leakage of myoglobin, CPK, uric acid, increased levels of C-reactive protein (CRP), and elevated serum and plasma levels of cell-free (cfDNA) (Breitbach et al. 2012).

Recently, Papayannopoulos and Zychlinsky (2009) reported "a new strategy for using old weapons" consisting of released nuclear DNA from neutrophils into the extracellular matrix, known as neutrophil extracellular traps (NETs). A pathogen-induced cell death was described, in which activated immune-competent cells enter a cell-death program, where the nuclear content decondense into the cytoplasm leading to NETs formation. The phenomenon of increased circulating cfDNA concentrations might be a hallmark of muscle death. cfDNA accumulation might reflect a kind of cell death similar to trap formation or active release of cfDNA as in overtraining-induced increases in cfDNA (Zhang et al. 2014). NETs may have an important role in muscle cell death similar to apoptosis or necrosis. The understanding of the mechanisms of skeletal muscle death may assist in the prevention of some processes that lead to this irreversible phase.

2 Muscle Terminology

The precise medical terminology of muscle pathology is somewhat confused and puzzled, resulting in abundance of terms. For instance,

muscle weakness, atrophy, and wasting may also be defined as myopenia, in which the volume of the sarcoplasm is decreased, leading to reduced muscle mass. The term dynapenia describes the decrease in myofibrillar size and protein synthesis that affects muscle strength. Moreover, some medical characteristics are also being used to describe muscle vitality and capability such as muscle mutability, which describes the muscle capacity to change its metabolic components (Rothstein and Rose 1982), or muscle malleability, which describes the ability to change muscle function according to requirements (Goldspink 1985). Finally, the term muscle symmorphosis describes the process of morphogenesis where structural elements are designed to satisfy a selective function (Weibel et al. 1991). The common ground of all these terms is muscle adaptability that basically is 'economically design-dependent'.

Skeletal muscle can undergo positive changes in response to various interventions and stimuli. These include physical training, resistance exercise, mechanical loading, electrical stimulation, or nutritional modifications mainly by dietary protein and essential amino acids (e.g., ~3 g/day of leucine) (Thalacker-Mercer and Drummond 2014). Moreover, skeletal muscle has some self-repair capabilities of mild internal damage. The intrinsic repairing system in skeletal muscle consists of endogenous satellite cells that are present in adult skeletal muscle. However, these self-repair capabilities may be affected by age, the type of the damage or injury, and by its severity (Yin et al. 2013).

Therefore, the ability of skeletal muscle to change itself, sometimes within minutes, can earn it a 'title' of the most adaptable tissue in human body. Yet it is worthwhile to note that some muscle fiber changes are reversible (hypertrophy and atrophy), some partially reversible (sarcopenia) (Mendelsohn and Larrick 2014), and some irreversible (dystrophy and cachexia) (Shin et al. 2013). An understanding of the fundamental roots of muscle tissue plasticity is essential for primary and secondary prevention. The purpose of this overview is to clarify the different mechanisms that lead to muscle death including apoptosis, autophagy, and necrosis. Moreover, pathological conditions in which increased muscle death is evident, such as cachexia and sarcopenia of aging, will be dwelled on.

3 Muscle Protein Synthesis and Degradation

Skeletal muscle is mostly protein-based dry tissue. It is in a constant state of protein turnover, architecture setting, and regular production of signal transduction molecules. Therefore, skeletal muscle can be described as a plastic tissue (Matsakas and Patel 2009). The term muscle plasticity refers to the muscle's ability to increase (hypertrophy), decrease (atrophy), or maintain a stable mass in response to changes in external/internal environment. Balance of muscle protein synthesis and degradation is divided into three categories: A stable state of muscle mass represents equilibrium between muscle protein synthesis and degradation. When synthesis is larger than degradation than muscle hypertrophy is present, and when synthesis is inferior to degradation than muscle atrophy occurs.

3.1 Muscle Protein Synthesis

It is widely accepted that increased rates of protein synthesis (>1.2 % day) result in increased myofibers area (Hood et al. 2006). The process of growth of skeletal muscle is only briefly tackled in this article. Certain amino acids serve as the building blocks for contractile proteins. Cytosolic amino acids arise from extracellular sources, *de novo* synthesis, or recycled proteins which are degraded by the ATP-dependent ubiquitin-proteasome system (UPS). The amino acids committed to the synthesis of new proteins are coupled with tRNA, forming aminoacyl-tRNA. Protein synthesis stops if any amino acids become rate-limiting.

3.2 Muscle Protein Degradation

While accelerated degradation of muscle proteins has gained importance for the progression of muscle wasting and weakness, the regulation of the process of muscle protein degradation in sarcopenia, rhabdomyolysis, poliomyelitis, or cachexia remains uncertain (Rai et al. 2014). Generally, protein degradation is regulated in different pathways, such as the UPS and lysosomal/autophagy systems. The mechanisms and pathways of skeletal muscle death and atrophy are described below.

4 Skeletal Muscle Death and Atrophy – Pathways and Mechanisms

Since skeletal muscle is a post-mitotic tissue, the pathways and mechanisms of muscle death are less clear as in other proliferative tissues. Generally, skeletal muscle can be induced to die *via* necrosis, autophagy, and apoptosis, depending on the stimuli and developmental programming of the cell (Sandri 2010). In addition, as a post-mitotic tissue, the size and mass of skeletal muscle is regulated by protein turnover.

4.1 Necrosis in Skeletal Muscle

Skeletal muscle necrosis is associated with inflammation and phagocytosis and is characterized by damage to a part of the myofiber. Muscle necrosis results in breakdown of the sarcolemma and fragmentation of the sarcoplasm (Kattapuram et al. 2005). Muscle necrosis is widely observed in different kinds of non-physiological conditions such as crush injury, extreme physical exercise (particularly when poorly hydrated and alcohol intoxicated), or in certain pathologies such as polymyositis, rhabdomyolysis (Zimmerman Shen 2009), muscular dystrophy, and cocaine influence and intoxication. Unlike apoptosis, necrosis represents passive irreversible cell injury or death without underlying regulatory mechanisms governed by a specific pattern of differential gene expression.

During muscle necrosis, the myofiber undergoes rupture of its sarcoplasma membrane followed by rapid intake of fluids and invaded cells from the extracellular matrix or bloodstream. These include an influx of sodium ions and neutrophils, along with the accumulation of alkaline phosphatase (ALP) around the fiber. The intracellular swelling leads to protein degradation and oxidative stress due to accumulation of reactive oxygen species (ROS), formation of abnormal mitochondria, hydrolysis of NAD^+, and depletion of ATP; which all leads to myofiber disintegration. Finally, potassium and phosphate ions, myoglobin, CPK, and uric acid are released into the bloodstream by the destroyed myofibers. A large family of cysteine proteases known as caspases plays an important role in the regulation of necrotic cell death (Ogata et al. 2009).

4.2 Autophagy in Skeletal Muscle

Autophagy is a physiological process by which, organelles and proteins are transported from the cytoplasm to the lysosome for degradation. This process is essential for removing damaged cellular components and remodeling cellular architecture (Neel et al. 2013). The autophagy system includes small ubiquitin-like molecules (LC3, GABARAP, GATE16, and Atg12) that are transferred from the conjugation system to the membrane for commitment to become a double-membrane vesicle (autophagosome) that engulfs portions of cytoplasm (Sandri 2010). Sequestered organelles and proteins are docked to the lysosomes for their degradation. Fusion of the outer membrane of the autophagosome with the lysosomal membrane determines the degradation of the inner membrane and the proteins that are associated with it (Sandri 2010). Autophagy is controlled by many cellular pathways and the evolutionary conserved autophagy-related genes (Atg). This process includes three main steps: (1) initiation, (2) nucleation (autophagosome formation), and (3)

lysosome fusion (degradation) (Wohlgemuth et al. 2010; Vergne et al. 2009). The initiation step of autophagy is regulated by nutrients/fasting that influence the insulin and insulin-like growth factor 1 (IGF-1) signaling pathways. Also, Bcl-2 and other members of the BH3 protein family regulate autophagy initiation by interacting with the beclin-1 nucleation complex. The nucleation step is regulated by the beclin-1 complex that initiates the nucleation of the phagophore by producing nucleating lipid species and initiating the elongation of the nascent phagophore. During the final step, the mature autophagosome is trafficked to the lysosome where fusion occurs. The cargo of the autophagosome can then be degraded by specific lysosomal enzymes in a structure called an autolysosome. Lysosomal lipases or glucosidases break down lipids and carbohydrates to their respective components, and a variety of hydrolases break down proteins into amino acids.

The accumulation of autophagosomes within myofibers is a common feature of various skeletal muscle diseases causing atrophy and dystrophy (Wohlgemuth et al. 2010). Compared to other tissues, skeletal muscle autophagy is both unique and difficult to study. The autophagosomes are the smallest in this tissue and upon autophagy activation they persist for up to 48 h, compared to only few hours in other tissues (Vergne et al. 2009). Although the main function of the autophagy process in skeletal muscle is secondary to catabolic conditions in which proteins are broken down to remove and eliminate unfolded and toxic proteins, as well as abnormal and dysfunctional organelles, its role in muscle death is indispensable. Recent reports suggested that autophagy also contributes to muscle wasting, and even causes positional alteration of myonuclei, which consequently generates muscle cell death (Penna et al. 2013). Thus, on the one hand, the autophagy process is an important mechanism that regulate muscle mass during catabolic conditions, but on the other hand, it is necessary for degeneration of contractile proteins leading to muscle death.

4.3 Apoptosis in Skeletal Muscle

Apoptosis is a highly coordinated process of programed cell death which takes place under physiological and pathological conditions (Marzetti et al. 2012; Otrocka-Domagała 2011). The main role of apoptosis is to eliminate redundant or metabolically exploited cells and to reduce the number of cells in case of excessive proliferation. Apoptosis may be induced by external stimuli that activate various molecular pathways of cell death, causing DNA degradation, damage to proteins, and structure and cell disintegration (Marzetti et al. 2012).

In highly proliferative tissues, apoptosis serves to maintain a constant number of cells and consistent tissue architecture, counterbalancing the rapid proliferation. However, in post-mitotic tissues such as skeletal muscle, the role of apoptosis is less clear. Also, with respect to cell death, skeletal muscle is a unique tissue because myofibers are multinucleated. This has led to the concept of the myonuclear domain, which is defined as the theoretical amount of cytoplasm supported by a single myonucleus. Thus, skeletal muscle represents a unique tissue with respect to apoptosis. Although, myofibers seem to be relatively resistant to harmful activity of pro-apoptotic factors, apoptosis is observed in various catabolic states including chronic heart failure, motor neuron disease and denervation, age-related sarcopenia, and myopathies induced by genetic and inflammatory factors or by myotoxic drugs (Kob et al. 2015).

Apoptosis can be induced by both extrinsic and intrinsic stimuli, with some cross-talk between these two signaling pathways (Marzetti et al. 2012). The apoptotic machinery includes regulatory proteins, endonucleases, protease inhibitors, and proteolytic enzymes, known as caspases. Upon stimulus for cell death, initiator caspases (caspases 8, 9, and 12) are engaged, leading to the activation of effector caspases (caspases 3, 6, and 7), which are responsible for cellular degradation and DNA fragmentation. The extrinsic signaling pathway of apoptosis is

triggered by the interaction of cell surface death receptors (tumor necrosis factor receptor, TNF-R) with their ligands (TNF-α) (Andrianjafiniony et al. 2010).

Apoptosis may also be stimulated by other death-inducing signals, such as ROS, reactive nitrogen species (RNS), imbalanced calcium regulation, and alterations in the composition and abundance of Bcl-2 family proteins, such as Bax, Bad, Bcl-2, and Bcl-xl (Dupont-Versteegden 2006). The intrinsic pathway of apoptosis involves the participation of mitochondria or the endoplasmic reticulum. Mitochondria can induce apoptosis independent of caspase activation through the release of apoptosis-inducing factor and endonuclease G, both of which can directly operate DNA fragmentation (Dam et al. 2012). In the nucleus, DNA fragmentation caused by activated endonucleases, chromatin condensation, and the breakdown of the nuclear envelope occurs and eventually the cell itself disintegrates into apoptotic bodies and is phagocytosed by surrounding cells.

Since myofibers are multinucleated, apoptosis in skeletal muscle displays some unique features. In contrast to other cells, a process of 'myonuclear apoptosis', consisting of the activation of the apoptotic cascade, results in removal of individual myonuclei and its relative portion of sarcoplasm (Marzetti et al. 2010). This process leads to fiber atrophy rather than the death of a whole cell. In addition, apoptotic signaling in skeletal muscle may stimulate degradation of muscle proteins through the activation of the UPS, leading to fiber atrophy without myonuclear removal. Skeletal muscle tissue is rich in mitochondria, which are the main site of ROS production. The level of ROS in skeletal muscles increases in response to contractile activity, ischemia/reperfusion, muscular dystrophies, and muscle ageing (Bar-Shai et al. 2008; Meng and Yu 2010; Janssen-Heininger et al. 2000). ROS can induce apoptosis directly and indirectly *via* the activation of transcriptional factors. Thus, the potential of ROS to induce oxidative damage has significant implications for the cellular integrity of highly metabolic, long-lived, and post-mitotic tissues such as skeletal muscle. Given the large share of mitochondria in the metabolism of muscle fibers, the mitochondrial pathway seems to play a key role in skeletal muscle apoptosis.

4.4 Paraptosis

Paraptosis is a form of programed cell death with a unique combination of certain apoptotic and necrotic characteristics (Danaila et al. 2013). Paraptosis does not demonstrate apoptotic morphology such as nuclear fragmentation, formation of apoptotic bodies, or definitive demonstration of chromatin condensation, all seen in apoptosis. Instead, paraptosis displays a somewhat primitive path of cell death, comparable to necrosis, including death characteristics of certain receptors: TNFR1, Fas/CD95, TRAIL-R, and Toll-like receptors (TLR3, TLR4), cytoplasmic vacuole formation, and late mitochondrial swelling and clumping. The number and size of autophagic vacuoles increase over time. Eventually, the size of vacuoles reaches a point of no return and the cell cannot recover (Kimura et al. 2007).

4.5 Ubiquitin-Proteasome System in Skeletal Muscle

The UPS is an ATP-dependent proteolytic system that involves the degradation of target proteins, with substrates identified for degradation by the addition of ubiquitin molecules, a process itself coordinated *via* the activity of a triplet of enzymes. Ubiquitin is first bound to the ubiquitin-activating enzyme (E1) *via* a high-energy thioester bond in the ATP-dependent process. Subsequently, ubiquitin is transferred from the E1 enzyme to the ubiquitin-conjugating enzyme (E2) *via* the formation of a new thioester linkage between ubiquitin and a cysteine residue of the E2 enzyme. Catalyzed by the action of an ubiquitin-ligase enzyme (E3), the ubiquitin monomer is conjugated to the target protein *via* an isopeptide bond between the amino group of lysine residue in the target protein and the

carboxyl terminal glycine residue 76 in Ub (Murton et al. 2008). In eukaryotic cells, only one E1 enzyme has been characterized. In humans, several dozens of E2 enzymes are also present, in addition to hundreds of E3 ligases through which target specificity is established (Murton et al. 2008). The specificity of the UPS is due to the ability of different E3s to recognize different degradation signals on the substrates. The process is repeated until a minimum of four ubiquitin monomers are covalently attached *via* lysine residue 48 of ubiquitin to the target protein. This classical formation is recognized by the 26S proteasome as a signal to degrade the target protein. Following successful ubiquitination, proteins are unfolded and fed into the proteasome in an ATP-dependent process.

A substantial body of evidence has accumulated implicating the UPS as the principal regulator of skeletal muscle atrophy. Findings from cell line, animal, and human studies have consistently pointed to the UPS as a pivotal component to the instigation and regulation of muscle protein breakdown. The increased expression of UPS constituents, including components of the 26S proteasome itself, and the prevention of increased proteolysis in atrophic conditions by the use of proteasome inhibitors, has led many to conclude that the UPS is intrinsically linked to the degradation of myofibril proteins in skeletal muscle.

In 2001, the mRNAs for two muscle-specific E3s were found to be elevated in the atrophied muscles of food-deprived mice and limb immobilized rats. These two E3s, muscle atrophy F-box (MAFbx/atrogin-1) and muscle RING finger-1 (MuRF1), were termed 'atrogenes', and increased mRNA levels for both have been observed in various animal models of muscle atrophy, including burn injury, diabetes mellitus, denervation, unweighting, dexamethasone administration, and sepsis (Kisselev and Goldberg 2001). The expression of MAFbx/atrogin-1 and MuRF1 is primarily confined to striated muscle (Foletta et al. 2011). The importance of these "atrogenes" in muscle wasting have been confirmed through knockout mice studies, where the absence of MAFbx/atrogin-1 or MuRF1 reduced denervation-induced muscle atrophy. When knocked out, MAFbx/atrogin-$1^{-/-}$ and MuRF$1^{-/-}$ mice appear resistant to the effects of denervation-induced muscle atrophy, with a 56 % and 36 % respective sparing of muscle loss, compared to controls (Andrianjafiniony et al. 2010). Thus, it has been suggested that MAFbx/atrogin-1 and MuRF1 may, in part, be responsible for the UPS mediated muscle protein degradation observed during muscle atrophy conditions.

The specific proteins that MAFbx/atrogin-1 and MuRF1 target for poly-ubiquitination and subsequent proteasomal degradation during skeletal muscle atrophy are still under investigation. Previous studies demonstrated that MAFbx/atrogin-1 targets myogenic transcription factors, which suggests a role for MAFbx/atrogin-1 in the regulation of myoblast differentiation. Elongation initiation factor 3 subunit 5 (eIF3-f) responsible for the initiation of protein synthesis, and MyoD which regulates muscle differentiation were found to interact with MAFbx/atrogin-1 and to be ubiquitinated and degraded in skeletal muscle. A decrease in eIF3-f causes skeletal muscle atrophy. Also, poly-ubiquitination of MyoD by MAFbx/atrogin-1 results in inhibition of MyoD-induced myotube differentiation and formation. Similar to MyoD, MAFbx/atrogin-1 mediates the poly-ubiquitination of myogenin, resulting in its degradation during dexamethasone-induced myotube atrophy (Foletta et al. 2011). In contrast to MAFbx/atrogin-1, previous studies suggest that MuRF1 interacts with structural proteins. MuRF1 binds titin and potentially mediates titin signaling. MuRF1 also binds and degrades MyHC proteins following the treatment of skeletal muscle with dexamethasone. Additionally, MuRF1 degrades myosin-binding protein C and myosin light chain (MyLC)-1 and MyLC-2 during denervation and fasting conditions. These studies suggest that MAFbx/atrogin-1 targets molecules regulating protein synthesis and muscle growth, whereas MuRF1 may act to control the level of protein degradation (Foletta et al. 2011).

4.6 Role of NF-κB in Skeletal Muscle Death and Atrophy

Many physiological conditions such as oxidative stress and aging have a direct catabolic effect on skeletal muscle, leading to muscle atrophy through inhibition of protein synthesis and an increase in protein degradation. In many cases the catabolic effect involves the up-regulation of the transcription factor NF-κB (Ahv and Aggarwal 2005; Glass 2005; Cai et al. 2004). NF-κB is a known regulator of genes that encode cytokines, cytokine receptors, and cell-adhesion molecules. These can modulate inflammatory responses and induce proteolysis and breakdown of myofibrillar proteins. NF-κB is a nuclear factor that binds to the promoter of the kappa chain of immunoglobulins in B cells. NF-κB is present in the cytoplasm of every cell type in its inactive state, and it is conserved in animals all the way from drosophila to humans. Five different mammalian NF-κB family members have been identified and cloned: NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), RelB, and c-Rel. All family members share a highly conserved Rel homology domain responsible for DNA binding, a dimerization domain, and the ability to interact with the intracellular inhibitor of NF-κB (IκB) (Ahv and Aggarwal 2005). Activation of NF-κB is controlled by the IκB kinase (IKK) complex. Upon phosphorylation by IKK, IκB is ubiquitinated and targeted to the proteasome for degradation, resulting in the activation of NF-κB (Glass 2005).

In resting cells, NF-κB, consisting of p50 and p65, is sequestered in the cytoplasm into the inactive form through its association with IκB-α. In response to environmental stimuli, including cytokine/chemokines, viral and bacterial pathogens, and stress-inducing agents the inactive NF-κB/IκB complex is activated by phosphorylation on two conserved serine residues within the N-terminal domain of IκB proteins. Phosphorylation of these residues in response to stimulators leads to the immediate poly-ubiquitination of IκB proteins. Subsequently, IκB proteins are targeted for rapid degradation by the 26S proteasome. Degradation of IκB unmasks the nuclear localization signal of NF-κB, which allows for a rapid translocation of NF-κB into the nucleus where it binds avidly to DNA (Cai et al. 2004). Activated NF-κB binds to specific DNA sequences in target genes, designated as κB-elements, and regulates transcription of over 400 genes involved in immune-regulation, growth regulation, inflammation, carcinogenesis, and apoptosis.

Numerous of studies have demonstrated that NF-κB is strongly up-regulated in muscle atrophy. This has been shown using immobilization studies in rodents, direct muscle injections of cytokines, such as TNF-α and interferon-gamma (INF-γ), and denervation of the sciatic nerve to induce muscle wasting. Indeed, inhibition of the NF-κB pathway in several atrophy models prevented muscle degeneration and myofiber death (Cai et al. 2004).

The role of NF-κB in muscle atrophy has also been demonstrated by its ability to regulate the expression of the muscle specific E3 ubiquitin ligase MuRF1. Cai et al. (2004) have shown that activation of NF-κB in muscle-specific transgenic expression of activated IKK (MIKK) mice induces significant atrophy due to an accelerated protein breakdown, which is mediated by the expression of MuRF1, but not that of MAFbx/atrogin-1. Pharmacological or genetic inhibition of the IKK-β/NF-κB/MuRF1 pathway reversed muscle atrophy. When MIKK mice are crossed into a MuRF1 null background, there is a significant reduction in muscle loss, which demonstrates that transcriptional activation of MuRF1 by NF-κB is a key step in NF-κB-induced atrophy. Therefore, the IKK-β/NF-kB/MuRF1 signaling pathway which is activated upon atrophic stimuli, activates NF-κB that induces atrophy through up-regulation of MuRF1 (Cai et al. 2004).

5 Non-apoptotic Programed Cell Death

This pathway of myofibers death can occur due to denervation, intracellular calcium overload, cytoplasmic vacuolization, and NETosis. Muscle

cell death in non-apoptotic programed pathway is distinct from classical apoptosis. In comparison to apoptosis, myofibers lose viability long time after the insult begins, the cell diameter is slowly decreased, and only a little nuclear DNA fragmentation is observed (Wang and Pessin 2013). This section will only describe netosis as the non-programed cell-death.

5.1 NETosis

NETosis is a state of cell death that includes the release of NETs (Papayannopoulos and Zychlinsky 2009; Zhang et al. 2014). In this novel mechanism of cell death, activated neutrophils enter a cell-death program, whereby the nuclear and granular membranes dissolve and the nuclear content decondense into the cytoplasm. Finally, the plasma membrane ruptures and chromatin decorated with granular proteins is released into the extracellular space (Breitbach et al. 2014).

As mentioned earlier, increased circulating concentration of cfDNA may represent an important marker of muscle death. The accumulation of cfDNA, involving trap formation or active release of cfDNA, may constitute a kind of cell death that is similar to the overtraining-induced increase in cfDNA (Papayannopoulos and Zychlinsky 2009). Therefore, NETs may have an important role in muscle cell death similar to apoptosis or necrosis.

6 Pathological Conditions of Skeletal Muscle Death and Atrophy

6.1 Sarcopenia

Sarcopenia, the loss of skeletal muscle mass and strength that occurs with advancing age, is a common impaired state of health, with a high personal toll and huge financial costs (Cruz-Jentoft et al. 2010; Cesari et al. 2014; Carmeli et al. 2012; Teixeira Vde et al. 2012; Marzetti et al. 2010). The risk factors and causes of sarcopenia include both intrinsic factors (systemic and physiological changes of aging) and extrinsic factors (mainly lifestyle habits). Intrinsic factors that contribute to the development of sarcopenia include the reduction in anabolic hormones (e.g., testosterone, growth hormone, and IGF-1), increased inflammatory activity as measured by cytokines, such as interleukin (IL)-1, IL-6, and TNF-α, accumulation of free radicals which leads to oxidative stress and muscle catabolism, alterations in muscle anatomy and metabolism (infiltration of fat and connective tissues, decrease in type 2 fiber size, mitochondrial dysfunction, and increased apoptotic activity in myofibers) (Cesari et al. 2014). Extrinsic factors of sarcopenia include dietary factors ("the anorexia of aging", inadequate protein intake, and vitamin D insufficiency), a sedentary lifestyle, use of catabolic medications such as glucocorticosteroids, alcoholism, and smoking (Cesari et al. 2014; Rom et al. 2012). Exercise is the primary strategy in the prevention and treatment of sarcopenia. Particularly, progressive resistance training, in which the external load is systematically increased as the person is able to work against a heavier load, has the greater effect of increasing muscle mass and strength and attenuates the development of sarcopenia in older people (Carmeli et al. 2012; Rom et al. 2012).

Different pathways of intracellular signaling are involved in the mechanisms of sarcopenia. These include apoptosis, increased protein degradation through autophagy, calcium-dependent proteases (calpains and caspases), and the UPS, as well as decreased activation of satellite cell, responsible for muscle regeneration (Teixeira Vde et al. 2012). Data from animal studies have shown that apoptosis in skeletal muscle is increased in aging and correlates with the loss of muscle mass and strength. The mitochondrial and TNF-α-mediated pathways are the main pathways of apoptosis in the aged muscles. Although studies in animal models support the role of apoptosis in sarcopenia, the evidence in humans is still sparse (Teixeira Vde et al. 2012).

Sarcopenia is a result of the imbalance between protein degradation and synthesis.

Interestingly, there is no consensus in animal models and in humans about the role of the different proteolysis mechanisms involved in sarcopenia. For instance, the involvement of the UPS, the major regulator of skeletal muscle atrophy, in sarcopenia differs between animal and human studies. Consistent increases in gene expression of the muscle specific E3 ligases of the UPS, MAFbx/atrogin-1 and MuRF1, have been observed in a wide range of animal models including diabetes, cancer, renal failure, denervation, unweighting, and glucocorticoid or cytokine treatment. However, the role of MAFbx/atrogin-1 and MuRF1 in the age-related muscle atrophy remains controversial (Otrocka-Domagała 2011). Clavel et al. (2006) have demonstrated the involvement of the UPS in sarcopenia of fast-twitch muscle by studying the *Tibialis Anterior* muscle of aged rats. The decline in muscle mass of aged rats is accompanied by an increase in the level of ubiquitin conjugates and in the mRNA level of both MuRF1 and MAFbx/atrogin-1. Altun et al. (2010) have evaluated the UPS in adult and old rats. The total level of the 26S proteasome, the content of ubiquitinated protein, and the MuRF-1 protein level were increased in the old muscles. However, the MAFbx/atrogin-1 level was lower in the old muscles. In addition, Edstrom et al. (2006) have found that the expression of both MAFbx/atrogin-1 and MuRF1 is suppressed in the gastrocnemius muscle of old rats when compared with adult animals. While there is a considerable amount of disagreement between studies, the animal literature, as a whole, supports the notion that MAFbx/atrogin-1 and MuRF-1 play contribute, to some extent, to the age-related decrease in muscle mass (Gumucio and Mendias 2013). In humans, the UPS appears to function as efficiently in old muscle as it does in adult muscle, and age-related increases in total intramuscular ubiquitin content have been reported. However, there are conflicting data regarding the molecular mechanisms that regulate ubiquitin-mediated proteolysis in human muscle. Several studies have found no changes in either MAFbx/atrogin-1 or MuRF1 mRNA levels in aged skeletal muscles (Edstrom et al. 2006). On the other side, elevated mRNA levels of MuRF1 have been found in skeletal muscle of older women when compared with young women, suggesting that there may be a gender effect with respect to MuRF1 during aging (Ebner et al. 2013). Overall, it is difficult to draw definitive conclusions at this time, especially given the difficulty in tracking the expression of MAFbx/atrogin-1 and MuRF-1 in longitudinal studies. However, increased level of intramuscular ubiquitin-conjugated proteins in aged skeletal muscle suggests that the UPS likely contributes to sarcopenia in humans (Johns et al. 2013). It is possible that sarcopenia in humans is different than in non-human species, since it involves defects in Akt-mammalian target of rapamycin (mTOR) and serum response factor (SRF)-dependent signaling and not in MAFbx/atrogin-1 and MuRF-1 or enhanced proteolysis.

6.2 Cachexia

Cachexia is a multi-factorial systemic and metabolic syndrome defined by continuous loss of skeletal muscle mass, with or without loss of fat mass. Cachexia cannot be fully reversed by conventional nutritional support and may lead to progressive functional impairment and increased death risk. Cachexia is associated with cancers, holocaust survivors, starvation, HIV, chronic heart failure, anorexia, inflammation, insulin resistance, chronic obstructive pulmonary disease (COPD), primary depression, malabsorption, hyperthyroidism, and chronic kidney disease (Johns et al. 2013; Bossola et al. 2001; Khal et al. 2005; Busquets et al. 2007). Although a depletion of both adipose and skeletal muscle tissues may occur in cachexia, the loss of muscle has the greatest impact on the function and quality of life and is associated with a poor outcome (Sakuma et al. 2015). The terms cachexia and sarcopenia must not be used synonymously. Cachexia implies weight loss, while sarcopenia means loss of muscle mass without weight loss. The loss of muscle mass in sarcopenia may be accompanied by a gain of fat mass. The

molecular mechanisms of cachexia and sarcopenia also differ. For instance, the importance of the UPS in cachexia is established, while there is conflicting evidence for its role in sarcopenia (Palus et al. 2014). In the pathophysiology of cachexia, the loss of muscle mass is a major cause of fatigue due to a decline in energy reservoir and reduced energy intake. The rate of muscle protein degradation is increased due to up-regulation of NF-κB and a reduction in anabolic stimuli.

In many acute models of cachexia, the UPS is thought to play a major role in the process of muscle atrophy. The activation of the UPS has been shown in various conditions of cancer cachexia. Bossola et al. (2001) have demonstrated that activation of the UPS is evident in gastric cancer patients by measuring increased levels of ubiquitin mRNA compared with controls. In addition, Khal et al. (2005) have found increased mRNA expression of the proteasome subunits C2 and C5 and the ubiquitin conjugating enzyme, E214k, in skeletal muscle of cachectic cancer patients with weight loss compared with patients without weight loss, with or without cancer. There is also evidence for the role of apoptosis in muscle wasting in cachectic patients. Busquets et al. (2007) have demonstrated that apoptosis is increased in skeletal muscle of cachectic gastro-intestinal cancer patients by an increase in muscle DNA fragmentation and in poly (adenosinediphosphate ribose) polymerase (PARP) cleavage, indicating the presence of apoptosis. The treatment and management of cachexia depend on the underlying causes. However, generally, the existing treatment options are very limited and in most cases cachexia is an irreversible condition.

7 Conclusions

This overview discussed the main mechanisms by which skeletal muscle cells die. There are different types of skeletal muscle cells and different pathways leading to their death. In the last two decades, various signaling pathways regulating skeletal muscle death have been revealed, and not surprisingly it is assumed that additional novel pathways and mechanisms are going to be discovered. A better understanding of the underlying mechanisms responsible for muscle death may assist in the development of future treatments for the prevention or attenuation of muscle cell death.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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