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ORIGINAL ARTICLE

Determinants of health-related quality of life of patients with type 2 diabetes and multimorbidity: a cross-sectional study

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Abstract

Purpose To examine the determinants of health-related quality of life (HRQoL) of patients with type 2 diabetes (PwD) and multimorbidity (MM) (at least one co-occurring condition besides T2D) among sociodemographic, disease-related, and MM variables and the association of MM with therapeutic targets.

Methods A total of 179 PwD attending primary care (PC) in Greece answered the 15 dimension HRQoL (15D) questionnaire between August 2019 and October 2020. Sociodemographic, disease-related, and MM characteristics were recorded. MM was categorized as concordant or discordant based on whether or not it was related to the pathophysiology of T2D. Independent predictors of the 15D score were examined in stepwise regression models among sociodemographic, disease-related, and MM variables and the association of MM with glycated hemoglobin (A1C) and low-density lipoprotein cholesterol (LDL-C) was assessed.

Results The mean 15D score was 0.85 ± 0.11 and the mean MM count was 4.3 ± 1.8. Significant predictors of a higher 15D score were male gender, married state, higher monthly income, and more physical activity. Significant predictors of a lower 15D score were employment, depression, musculoskeletal disease, coronary artery disease, neuropathy, and MM count, but discordant had a stronger effect than concordant MM. Increasing MM count was not significantly correlated with A1C and was correlated with lower LDL-C.

Conclusion Non-medical (physical activity and sociodemographic) rather than disease-related characteristics and discordant more than concordant co-occurring conditions affected HRQoL of multimorbid PwD who did not have worse (A1C) or achieved better (LDL-C) therapeutic targets. A generalist approach to the non-medical needs and overall health conditions of PwD could be promoted in PC within the social determinants of health and MM.

Keywords Health-related quality of life · Multimorbidity · Social determinants of health · Type 2 diabetes mellitus · Primary care · Greece

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Introduction

The physical and psychosocial burden of living with diabetes is often challenging, affecting self-care behaviors, glycemic control, risk of complications, and quality of life (QoL) [1, 2]. Health-related QoL (HRQoL) is a multidimensional concept comprising an individual's subjective perception of physical, emotional, and social components related to illness or treatment [3]. Measurement of HRQoL in diabetes has for long been acknowledged as "the ultimate goal of all health interventions" [1] and, in the current patient-centered philosophy of diabetes care, as an important predictor of health outcomes and a priority of public health [2].

People living with diabetes have lower HRQoL compared to those without diabetes [4–7] or even compared to people with prediabetes [7]. Diabetes seems to lower HRQoL mainly with the coexistence of other chronic diseases [5, 8], and particularly in an additive manner [8]. This combination of a chronic disease with at least one other disease in a given individual defines multimorbidity (MM) which, in turn, may modify health outcomes and lead to frailty, increased disability, and decreased QoL [9]. Diabetes is among the most common starting conditions in the accumulation of later MM [10] and MM is more prevalent in patients with type 2 diabetes (T2D) (the most common form of diabetes worldwide) than in patients without T2D [11].

The literature on the association of QoL with diabetes-specific characteristics has been mixed [1]. For example, good glycemic control is may be linked to better QoL provided that treatment burden and hypoglycemia range low [1]. On the other hand, QoL in diabetes is firmly associated with numerous sociodemographic factors such as income, marital status, or gender [1]. The non-medical, social, and economic factors that affect health status constitute the social determinants of health (SDoH) that have been found to significantly impact therapeutic targets and QoL in T2D [12]. More importantly, the latest consensus guidelines for the management of T2D introduced the SDoH (e.g., education, income, occupation, living and working conditions, etc.) as factors to be addressed in a holistic, person-centered approach in order to prevent complications and optimize QoL [13].

In parallel, recent data report that increasing MM count in patients with T2D (PwD) is associated with higher all-cause mortality [14, 15] and hypoglycemia [14], but, the literature on its association with glycemic control is mixed [14]. Furthermore, recent cohort studies indicate that increasing MM count in T2D is either not associated with glycated hemoglobin (A1C) [16] or is associated with lower A1C [15, 17, 18], making poor glycemic control unlikely to explain the increased mortality observed in multimorbid PwD [14–16]. Instead, severe hypoglycemia has been demonstrated to be associated with increased mortality in multimorbid patients with diabetes [19].

The above data appear to emphasize the need for a shift of T2D management from a "single-disease model" approach toward a generalist approach of the complex needs of PwD and MM [11, 14, 20, 21], within the context of the socioeconomic problems that the patients may face [20, 21], thus offering the potential to improve health outcomes and QoL [20]. The aforementioned paradigm shift that focuses on the person and not on the disease particularly characterizes primary care (PC), which deals with a wide range of health problems and PC providers, who can be regarded as experts in dealing with MM in parallel with the geriatricians' expertise in secondary care [21]. Specifically regarding Greece, only a few studies [22, 23] conducted in PC have examined the determinants of HRQoL of PwD, while data on the association of MM with therapeutic targets are lacking.

Given this evidence, the primary outcome of the present study was to examine the determinants of HRQoL among sociodemographic, disease-related, and MM characteristics in PwD in urban PC in Greece. The secondary outcome was to examine the relationship of MM with A1C and low-density lipoprotein cholesterol (LDL-C), two main therapeutic targets of T2D [13].

Methods

Study design, setting, and participants

This cross-sectional study took place in a local health team unit, an urban PC setting of a city of Greece with a population of 23,000. The data were collected during August 2019 to March 2020 and May-October 2020 due to the COVID-19 pandemic restrictions. The participants were adult (≥ 18 years old) ambulatory outpatients with a diagnosis of T2D of at least 6 months, registered in the study setting, and presenting for any medical reason related to diabetes. Further inclusion criteria were willingness to participate in the study and ability to communicate in Greek and complete questionnaires. Patients with other forms of diabetes, transplantation, active cancer, poor overall health, dementia, psychosis, and bipolar disorder were excluded.

Data collection

Upon informed consent, persons eligible and willing to participate were asked a series of questions regarding their background data, such as age, marital status, years of education, employment, monthly income, smoking habits, vaccination status, physical activity level, duration of T2D, insulin use, number of episodes of hypoglycemia during the

last 6 months, and number of times self-monitoring of blood glucose (SMBG) was performed per week. Medical history regarding co-occurring conditions besides T2D (MM) was obtained. Data derived from the clinical examination, i.e., body mass index (BMI) (weight (Kg)/height (m^2)) and waist circumference, were recorded. Recent laboratory results (until up to 6 months before), i.e., A1C, lipid profile, serum creatinine, and urine albumin creatinine ratio (ACR), were gathered. Finally, the participants answered the Greek version [24] of the 15 dimensions (15D) questionnaire for the assessment of HRQoL via assisted report by another researcher who collected the data blindly from the other researchers. The data were coded and only the researchers had access to them.

The co-occurring conditions were divided according to Piette and Kerr's [20] typology of diabetes comorbidities in concordant to T2D (related to the pathophysiology of the index disease and sharing a common treatment approach) and discordant to T2D (unrelated to the pathophysiology of the index disease and not sharing a common treatment approach).

Concordant MM included the following: (i) hypertension (history or use of any antihypertensive medication), (ii) dyslipidemia [25] or the use of statin/fibrate, (iii) coronary artery disease, (iv) stroke or transient ischemic attack, (v) peripheral artery disease (carotid artery disease (as assessed by duplex ultrasound or revascularization) or lower extremity artery disease (as assessed by duplex ultrasound or revascularization or self-reported intermittent claudication)), (vi) self-reported retinopathy related to T2D diagnosed by an ophthalmologist, (vii) self-reported peripheral neuropathy (a positive answer in the question: "do you feel numbness, tingling, burning, or sharp pain in feet or hands, especially at night, that bothers you"?), (viii) nephropathy (estimated glomerular filtration rate < 60 ml/min/1,73 m^2 or urine ACR > 30 mg/g at two visits 90 days apart) [25], (ix) heart failure, (x) atrial fibrillation, and (xi) obesity (BMI ≥ 30 Kg/m^2).

Discordant MM included the following: (i) musculoskeletal disease (osteoarthritis or self-reported chronic low back pain or spine surgery or rheumatic arthritis (osteoporosis was excluded unless it was complicated with fracture), (ii) respiratory disease (chronic obstructive pulmonary disease or asthma), (iii) cancer, and (iv) self-reported depression diagnosed by a health-care provider.

The co-occurring conditions collected were limited to those described above due to the time constraints of a short appointment and accuracy of diagnosis. The Declaration of Helsinki [26] ethical principles for research involving humans were applied throughout the study.

Table 1 Data on sociodemographic and disease-related characteristics for the 179 patients with type 2 diabetes included in the study

Parameter	*N* (%) or mean ± SD
Age (years)	67.7 ± 9.2
Gender (female)	79 (44.1)
Marital status (married)	134 (74.9)
Years of education	8.9 ± 3.9
Employment (employed)	21 (11.7)
Monthly income (< 800€)	120 (67.0)
Smoking	43 (24.0)
Physical activity (< 30 min 3 times per week)	113 (63.1)
Anti-influenza vaccination	115 (64.2)
Anti-pneumococcal vaccination	63 (35.2)
Duration of diabetes (years)	10.7 ± 8.9
Body-mass index (Kg/m^2)	32.2 ± 5.8
Insulin use	26 (14.5)
Hypoglycemia episodes (last six months)	0.8 ± 2.5
A1C (< 7%)	110 (81.5)
Waist circumference (cm)	109.0 ± 12.5
Self-monitoring of blood glucose (per week)	5 ± 5.7

Evaluation instrument

15 dimensions (15D)-HRQoL questionnaire

The 15D questionnaire is a generic, standardized, multidimensional measure of HRQoL [3]. It includes 15 dimensions (questions) regarding the following: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity [3]. Each dimension is divided into five levels of functional status and the questionnaire can be presented as a 15-dimensional profile or interpreted as a 15D index score (single index number) for every dimension or over all the dimensions [3]. The maximum score is 1 (no problem on any dimension-perfect HRQoL) and the minimum score is 0 (being dead) [3]. The Greek version of the 15D questionnaire has been validated in a sample of patients with coronary artery disease [24]. The reason for using the 15D questionnaire was that it has been proven to have increased discriminating ability for coronary artery disease and retinopathy in Greek PwD compared with other generic instruments [27]. The original author [3] granted us permission to use the 15D questionnaire, provided us with the Greek translation [24], and interpreted the data on a 15D index score.

Statistical analysis

Categorical variables are presented as absolute and percentage frequencies, while continuous variables are described with their means and standard deviations. The dependence of the 15D score on the covariates depicted in Tables 1 and 2 was examined using stepwise linear regression models. All binary variables were recorded as 0 (No) and 1 (Yes)

and were used as independent predictors of the 15D score in a stepwise linear regression model. Independent samples t-tests were also performed. The association between total MM count and the levels of A1C and LDL-C is reported with Spearman's rho correlation coefficient (ρ). The level of significance was set at $p < 0.05$. Data were analyzed using Statistical Package SPSS, version 28.0 Armonk, NY, IBM Corp.

Results

The final study sample consisted of 179 multimorbid PwD (who had at least one other co-occurring condition), 132 of whom were enrolled between August 2019 and March 2020 and 47 between May and October 2020. The age range was 43–87 years old. The responses in the 15D questionnaire were 177. Five participants belonged to an ethnic minority. No participant had any diabetic foot complication or renal/heart/liver end stage disease or was infected by SARS-COV-2 throughout the study.

Table 1 presents background data on sociodemographic and disease-related characteristics and Table 2 summarizes data on all MM counts. The mean A1C was 6.9%±1.3 and the mean LDL-C was 100.2 ± 33.1 mg/dL. The frequency of the co-occurring conditions was 3% for 1, 13% for 2, 20% for 3, 22% for 4, and 45% for ≥ 5 (maximum 10).

Table 3 displays data on index scores of the 15D questionnaire. As can be seen, the item "Eating" did not convey any information differentiating the subjects, as all the responses were the at the best level. Almost the same can be said regarding the item "Speech". It is possible that other responses aside from the best level did not reflect situations that apply to the current study sample as it was composed of individuals with overall good health. The mean values of the 15D scores were significantly lower for discordant than for concordant MM for most of the 15 dimensions.

Cronbach's alpha reliability coefficient was 0.836 (95% CI 0.798–0.869), which means that the 15 items had quite satisfactory internal consistency.

The 15D score did not follow a normal distribution; nevertheless, parametric procedures were mostly applied. The difference in the mean 15D score between male ($N = 98$, 0.883 ± 0.102) and female ($N = 79$, 0.818 ± 0.119) participants was statistically significant ($t_{177} = 3.88$, $p < 0.001$). This means that men reported an overall better HRQoL than women. The value of Cohen's d of 0.586 signifies that gender had a moderate effect size on the 15D score. Marital status also had a significant effect ($p = 0.032$) on the 15D score, with married subjects reporting a better HRQoL compared to single/divorced/windowed, although the effect size was smaller (Cohen's d = 0.377). Monthly income and employment also had a significant effect, but it seems that gender remained the most important. Physical activity had a significant effect on its own.

The negative coefficients mean that the presence of a co-occurring condition lowered the value of the 15D score. For example, depression on average lowered the 15D score by 0.078 units, neuropathy by 0.056, coronary artery disease

Table 2 Data on absolute and percentage frequencies and mean values of concordant, discordant and total multimorbidity (MM) count

Co-occurring conditions	*N* (%) or mean ± SD
Concordant MM	179 (100), 3.6 ± 1.5
Hypertension	140 (78.2)
Dyslipidemia	176 (98.3)
Coronary artery disease	35 (19.6)
Stroke/Transient ischemic attack	12 (6.7)
Peripheral artery disease	30 (16.8)
Retinopathy	17 (9.5)
Neuropathy	49 (27.4)
Nephropathy	38 (21.2)
Heart failure	21 (11.7)
Atrial fibrillation	15 (8.4)
Obesity	105 (58.7)
Discordant MM	101 (56.4), 0.7 ± 0.8
Musculoskeletal disease	68 (38.0)
Respiratory disease	20 (11.2)
Cancer	17 (9.5)
Depression	29 (16.2)
Total MM	179 (100), 4.3 ± 1.8

Table 3 Data on the mean index score of the 15 dimensions (15D) questionnaire for the total and the dimensions. Comparisons between all patients with discordant multimorbidity (MM) (and concordant) ($N = 99$) and patients with only concordant MM ($N = 78$) with the independent samples t-test (mean ± SD)

Dimension	Total MM ($N = 177$)	Concordant MM ($N = 78$)	Discordant MM ($N = 99$)	*p*-value
15D total	0.85 ± 0.11	0.90 ± 0.08	0.81 ± 0.12	< 0.001
Mobility	0.86 ± 0.17	0.94 ± 0.12	0.80 ± 0.18	< 0.001
Vision	0.90 ± 0.17	0.92 ± 0.14	0.88 ± 0.19	0.110
Hearing	0.91 ± 0.16	0.92 ± 0.15	0.90 ± 0.17	0.283
Breathing	0.79 ± 0.19	0.82 ± 0.16	0.76 ± 0.21	0.034
Sleeping	0.78 ± 0.25	0.88 ± 0.15	0.71 ± 0.28	< 0.001
Eating	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	-
Speech	0.97 ± 0.09	0.98 ± 0.07	0.97 ± 0.09	0.282
Excretion	0.89 ± 0.18	0.91 ± 0.18	0.88 ± 0.18	0.393
Usual activities	0.89 ± 0.19	0.94 ± 0.12	0.85 ± 0.23	< 0.001
Mental function	0.88 ± 0.19	0.90 ± 0.18	0.87 ± 0.20	0.358
Discomfort and Symptoms	0.88 ± 0.20	0.95 ± 0.12	0.82 ± 0.22	< 0.001
Depression	0.80 ± 0.25	0.89 ± 0.19	0.72 ± 0.27	< 0.001
Distress	0.69 ± 0.27	0.77 ± 0.23	0.62 ± 0.29	< 0.001
Vitality	0.82 ± 0.23	0.90 ± 0.15	0.76 ± 0.27	< 0.001
Sexual activity	0.59 ± 0.37	0.72 ± 0.34	0.48 ± 0.36	< 0.001

by 0.053 units, and musculoskeletal disease by 0.038 units, while employment lowered the 15D score by 0.048 units. In contrast, subjects with higher monthly income and more physical activity had higher scores (Table 4). Likewise, the presence and number of discordant MM had a more important negative effect on the 15D score than the presence and number of concordant MM (Table 5).

Finally, Spearman's rho correlation coefficient between MM count and A1C was not significant (ρ = 0.078, p = NS), while with LDL-C it achieved statistical significance (ρ=-0.187, $p = 0.016$). The correlation coefficient had a negative sign, meaning that increasing MM count was associated with lower LDL-C values.

Table 4 Statistically significant results for the linear regression model of the index score of the 15 dimensions (15D) questionnaire as the dependent variable on sociodemographic, disease-related and multimorbidity characteristics

Predictor	Coefficient	SE	t	*p*-value
Constant	0.921	0.024	37.752	< 0.001
Depression	-0.078	0.020	-3.912	< 0.001
Physical activity	0.041	0.016	2.559	0.011
Musculoskeletal disease	-0.038	0.016	-2.407	0.017
Neuropathy	-0.056	0.017	-3.314	0.001
Coronary artery disease	-0.053	0.020	-2.675	0.008
Monthly income	0.042	0.016	2.588	0.011
Employment	-0.048	0.023	-2.080	0.039

$R^2 = 0.343$

Table 5 Linear regression model of the 15 dimensions (15D) index score as the dependent variable on concordant and discordant multimorbidity (MM)

Predictor	Coefficient	SE	t	*p*-value
Constant	0.963	0.020	48.791	< 0.001
Discordant MM	-0.055	0.010	-5.638	< 0.001
Concordant MM	-0.019	0.005	-3.750	< 0.001

$R^2 = 0.242$

Discussion

Regarding sociodemographic characteristics, the male participants of the present study reported better HRQoL than the female, a finding that is well-established both in people with diabetes [1, 22] and in the general population [28]. This can be attributed to the existing gender differences in health and well-being, as women live longer than men but are disadvantaged in almost all dimensions of HRQoL [28]. Perhaps western societies still raise structural and cultural barriers to women's equality in social status and personal resources [28]. Since women rank the perception of their health significantly lower than men, it is important that their under-representation in the recent outcome trials [13] be checked and corrected [1].

In this study, married participants and participants with higher income reported better HRQoL. Likewise, a study conducted in a diabetes-specific clinic in Greece showed that living alone was an important determinant of lower diabetes-specific QoL in T2D [29]. In any case, having higher income and being married, which conceivably mean that a person is less socioeconomically deprived and less lonely, are among the most well-defined sociodemographic determinants of higher HRQoL in diabetes [1].

Given the negative impact of unemployment on psychological and physical health and its association with risk of suicide [30], the finding that employed participants had lower HRQoL seems paradoxical. On the other hand, a recent meta-analysis from China showed that workers reported lower HRQoL than the general population [31]. The authors attributed this difference to the ergonomic, environmental, and psychological hazards of harsh working conditions [31], which perhaps may apply to the working participants of our study as they are mainly employed in industry and agriculture. Furthermore, as they are younger than the retired coparticipants, the combination of both work and diabetes may create a burden in their lives. Marital status, monthly income, and employment, which were found to affect HRQoL in this study sample, are sociodemographic, non-medical characteristics that may parallel the SDoH of a holistic, person-centered approach in the management of T2D [13]. Lastly, physical activity had a significant effect on HRQoL, reflecting the beneficial effects of the continuum of human movement in T2D [13]. Since physical activity is a health behavior characteristic and a modifiable predictor of HRQoL, a special effort should be made to convince PwD to increase their physical activity or engage in an exercise program.

In the context of the management of patients with MM in PC, it has been proposed that three meaningful clusters of condition factors can be identified and grouped, namely, a cardiometabolic condition factor, a mental health condition factor (such as depression or anxiety), and a painful condition factor [32]. This might apply to the multimorbid PwD of the present study, since coronary artery disease, depression, and two painful conditions (musculoskeletal disease and neuropathy) were associated with lower HRQoL. This has also been demonstrated for coronary artery disease [4, 5], depression [4], and musculoskeletal disease [5, 8] in multimorbid PwD. A history of depression had the strongest negative effect on HRQoL in this study sample, this potentially directing our practice toward prioritizing the treatment of depression given that the latter deteriorates the ability of multimorbid patients to manage their other chronic conditions [32].

According to the Piette and Kerr's [20] typology of diabetes comorbidities, asymptomatic chronic conditions

(e.g., dyslipidemia or moderately poor glycemic control), although implicated in early mortality, are perceived by patients as less important. In contrast, symptomatic chronic conditions (e.g., depression or angina) are mainly involved in patients' functioning, symptom profile, and QoL [20]. Similarly, all the co-occurring conditions identified as negatively affecting HRQoL in this study could be characterized as symptomatic and, since discordant MM is mainly symptomatic, it could possibly exert a more prominent negative effect on HRQoL. Thus, discordant MM should not be overlooked in favor of concordant MM, namely, cardiovascular disease [15, 21], especially since recent data highlight the fact that discordant MM mainly contributes to mortality in T2D [33]. Moreover, the high prevalence of discordant MM found in the present study (56.4%) as well as in others [11, 16, 21] might imply that the T2D population is heterogeneous rather than typical and co-occurring conditions are a personal rather than a disease-related characteristic [21].

MM of PwD is associated with higher all-cause mortality [14, 15] and hypoglycemia [14] but reports on its association with A1C are mixed [14]. We showed that increasing MM count is not associated with A1C but is instead associated with lower LDL-C, a finding consistent with recent research [16, 17]. Since higher A1C and LDL-C are surrogate markers of worse health outcomes, our finding appears paradoxical; however, MM has recently been shown to be associated even with lower A1C [15, 17, 18], although in a large study this was observed in older PwD treated with insulin and thus predisposed to hypoglycemia [18]. Our finding that multimorbid PwD achieve equal A1C, while lower LDL-C could reflect patients' and clinicians' desire and efforts to slow the progression of preexisting or prevent the onset of new T2D-related MM [18]. Furthermore, it could be driven by the receiving of better quality of healthcare [34] or a higher utilization of healthcare [15, 20], offering multimorbid patients earlier diagnosis of T2D [15] or more opportunities for T2D-related monitoring and counseling, resulting in attainment of equal or even better therapeutic targets [15, 20]. These benefits could apply provided that inappropriate intensification of therapy in older multimorbid PwD [18] and hypoglycemia [14, 18, 19] can be avoided. The latter could be achieved especially in PC where patients with MM can be assured of continuity of care by a named doctor [31], this policy having very recently been legislated in Greece in the form of patient registration with a "personal doctor" [35].

In the present study sample, many non-medical factors, including a health behavior characteristic (physical activity), and sociodemographic characteristics (gender, marital status, employment, and monthly income) rather than disease-related characteristics (e.g., A1C, insulin use or vaccination) influenced HRQoL, corresponding to the SDoH. Furthermore, increasing MM count lowered HRQoL, but discordant MM had a stronger effect than concordant, implying a generalist perspective of the full range of health conditions the PwD may be living with, especially since they attained equal (A1C) or even better (LDL-C) therapeutic targets. The main strength of this study is that it has examined the association of A1C and LDL-C with as many co-occurring conditions as could be gathered during a short consultation, the results indicating that MM might not be an obstacle to the effective management of T2D. The current study also has a number of limitations, including the use of a generic instrument for the assessment of HRQoL instead of a diabetes-specific one that addresses more diabetes-related issues, which factor possibly influenced the non-significant association of A1C and HRQoL. Other limitations, due to the COVID-19 restrictions, are the relatively small sample size, the lack of power analysis for the sample size calculation, and the fact that one third of the study sample was recruited at the beginning of the COVID-19 crisis, which may have negatively influenced the QoL of PwD. Thus, our results should be interpreted with caution.

Conclusion

In multimorbid PwD attending PC in Greece, non-medical factors such as physical activity and sociodemographic characteristics rather than disease-related characteristics influenced HRQoL. Both concordant and discordant MM lowered HRQoL, but discordant MM had a more prominent effect. Despite the negative impact of MM on mortality, increasing MM count was not associated with A1C levels and was associated with lower LDL-C levels. A generalist approach to the non-medical needs and overall health conditions of PWD could be promoted in PC in the context of the SDoH and MM.

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Data availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval Approval was obtained from the Ethics Committee of the 5th Regional Health Authority of Thessaly and Sterea, Central Greece. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Competing interests The authors have no relevant financial or non-financial interests to disclose, except that Dr. Stavroula A. Paschou is an Associate Editor of Hormones journal.

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