Adiponectin as Biomarker of Osteoporosis 38

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V.B. Patel, V.R. Preedy (eds.), *Biomarkers in Bone Disease*, Biomarkers in Disease: Methods, Discoveries and Applications, DOI 10.1007/978-94-007-7693-7_9

Abstract

Adiponectin is one of the adipose tissue hormones synthesized and released mainly by mature adipocytes of visceral white adipose tissue. So far, scientific studies have been focused on the effect of adiponectin on regulation of glucose and fatty acid metabolism and its connection to cardiovascular system diseases and diabetes mellitus as well as the occurrence of metabolic syndrome. The latest reports indicate that this hormone is expressed not only on hepatocytes, endothelial cells, skeletal muscles, and central nervous system but also on osteoblasts, as shown by the presence of its specific membrane receptors (AdipoR1 and AdipoR2). Based on many reference data, it seems that adiponectin may be a link connecting the metabolism of adipose tissue and bone tissue. Due to its connection to bone turnover markers, it is a potential marker of osteoporosis.

Keywords

Adiponectin • AdipoR1 • Adipo R2 • Osteogenesis • Osteoporosis

List of Abbreviations

5′AMP	Activated protein kinase 5′
ACC	Acetyl-CoA carboxylase
Acrp30	Adipocyte complement related protein of 30 kDa
AdipoQ	Adiponectin, C1Q and collagen domain containing
AMPK	AMP-activated(-related) protein kinase
AN	Anorexia nervosa
apM1	Adipocyte most abundant gene transcript 1
BMD	Bone mineral density
BMI	Body mass index
BN	Bulimia nervosa
DHEA-S	Dehydroepiandrosterone sulfate
ERA	Early rheumatoid arthritis
FM	Fat mass
GBP	Gastric bypass surgery
GBP28	Gelatin-binding protein of 28 kDa
GDM	Gestational diabetes mellitus
GIGT	Gestational impaired glucose tolerance
GR	Glucocorticoid receptor
HMW	High molecular weight complex
IGF-1	Insulin-like growth factor 1
IGF-2	Insulin-like growth factor 2
IL-6	Interleukin 6
LAGB	Laparoscopic adjustable gastric band
LMW	Low molecular weight trimer-dimer
MAPK	Mitogen-activated protein kinase

MCP-1	Monocyte chemotactic protein
MMP-3, MMP-9	Matrix metalloproteinase 3 and 9
MMW	Middle molecular weight
MP	Metabolic phenotype
NOS2	Nitric oxide synthase 2
NTG	Normal glucose tolerance
OA	Osteoarthritis
OGL	Oral glucose load
OPG	Osteoprotegerin
PCOS	Polycystic ovary syndrome
PPAR	Peroxisome proliferator-activated receptor
PPAR-α	Peroxisome proliferator-activated receptor alpha
RA	Rheumatoid arthritis
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
RYGB	Roux-en-Y gastric bypass
SHBG	Sex hormone binding globulin
SREBP	Sterol regulatory element-binding protein
T1DM	Diabetes mellitus type 1
T2DM	Diabetes mellitus type 2
TAL	Total adiponectin level
TNF-α	Tumor necrosis factor alpha
UA	Undifferentiated arthritis
VBG	Vertical banded gastroplasty

Key Facts of Adiponectin

Adiponectin is one of the adipose tissue hormones synthesized and released mainly by mature adipocytes of visceral white adipose tissue and to a lesser extent by adipocytes of peripheral adipose tissue and bone marrow. It circulates in three different forms: high molecular weight (18-36mer), low molecular weight (hexamer), and a trimeric form. Adiponectin level is inversely related to visceral fat along with body mass index and positively related with biochemical markers of bone loss. Concentration of adiponectin varies greatly among even in subjects with similar BMIs, and the literature shows that this hormone depends on sex and is higher in women than in men.

Specific correlations between adiponectin and other biochemical parameters during osteoporosis should give useful information and determine the role of adiponectin in progression or inhibition of osteoporotic changes. Sadly, basing on current knowledge, adiponectin cannot be used as a clear-cut predictive marker for osteoporotic fracture risk, because its concentration changes not only during osteoporosis but in different medical conditions associated with inflammation or weigh loss too.

Definition of Words and Terms

Adiponectin	A polypeptide composed of 244 amino acids with a molecular weight of approximately 30 kDa being synthesized and released mainly by mature adipocytes of visceral white adipose tissue. Adiponectin MRNA has been identified, among others, in hepatocytes, endothelial cells, skeletal muscle, central nervous system, and osteoblasts.
AdipoR	Specific membrane receptor of adiponectin occurring in two isoforms: AdipoR1 and AdipoR2.
Anorexia (AN, anorexia nervosa)	is a type of psychosomatic disorder in which a sick person subjectively assesses his/her body weight as too high, resulting in extreme cachexia through very restrictive diet.
apM1 (ACDC)	Adiponectin gene.
Bone remodeling	is an active and dynamic lifelong process where mature bone tissue is removed from the skeleton (bone resorption) and new bone tissue is formed (bone formation). The remodeling cycle consists of three consecutive phases: resorption, reversal, formation and involves the removal of mineralized bone by osteoclasts followed by the formation of bone matrix through osteoblasts.
Cell differentiation	Process by which cells become progressively more specialized to possess a more distinct form and function.
Mesenchymal stem cells (MSCs)	Multipotent stromal cells that can differentiate into a variety of cell types such as: osteoblasts, chondrocytes, myocytes, adipocytes.
Osteoporosis	Very heterogeneous disease process, dependent on many causative factors, being characterized by low bone mass and deterioration of bone tissue, leading to increased bone fragility and risk of bone fractures (mainly hip, spine, wrist, and shoulders).
Peroxisome proliferator-activated receptor gamma 2 (PPAR©2)	Group of nuclear receptor proteins that function as transcription factors regulating the expression of genes, play essential roles in the regulation of cellular differentiation, development, and metabolism.

Transforming growth factor beta (TGF-β)	Secreted protein, type of cytokine that controls proliferation, cellular differentiation, and other functions, is part of a superfamily of proteins known as the transforming growth factor beta superfamily.

Introduction

There has been increased interest in adipose tissue as an endocrine organ, and several of these secreted proteins, termed adipokines, are currently undergoing extensive study regarding roles as divergent as feeding behavior to osteoporosis protection (Pajvani et al. 2003; Kontogianni et al. 2004; Richards et al. 2007).

Adiponectin was identified and later described independently by four research teams (1995–1996) to what it owes equivalent names being in use: Acrp30 (*adipocyte complement related protein of 30 kDa*), AdipoQ (*adiponection*, *C1Q*, *and collagen domain containing*), GBP28 (gelatin-binding protein of 28 kDa), and apM1 (*adipocyte most abundant gene transcript 1*) (Scherer et al. 1995; Hu et al. 1996; Maeda et al. 1996; Nakano et al. 1996).

Adiponectin is an adipocyte-specific secretory protein produced by differentiated adipocytes and its concentration is observed in a relatively large amount in human serum. This protein plays an important role in the regulation of glucose and fatty acid metabolism in the liver and muscles, and its activity may be connected to bone structure and human osteoblastic proliferation (Hu et al. 1996; Pajvani et al. 2003). The aim of this study is to show the importance of adiponectin as a potential marker of osteoporotic lesions.

Adiponectin – Basic Information

Biosynthesis, Structure, Target Tissues

Adiponectin is synthesized and released mainly by mature adipocytes of visceral white adipose tissue, although its expression is also observed in brown adipose tissue. Recent reports have indicated that adiponectin mRNA is identified in hepatocytes, endothelial cells, skeletal muscle, central nervous system, and osteoblasts (Berner et al. 2004).

Human adiponectin is biosynthesized as a polypeptide being composed of 244 amino acids with a molecular weight of approximately 30 kDa, 17 of which are a signal sequence, the cleavage of which is followed by formation of mature protein with a molecular weight of 28 kDa (Scherer et al. 1995; Hu et al. 1996; Maeda et al. 1996). It is characterized by a complex structure which consists of an N-terminal signal sequence, a short variable section not showing homology with

any other protein, a globular subunit situated on the carboxyl terminus, and a fibrous domain located on the amine terminus (Maeda et al. 1996; Kershaw and Flier 2004). A globular domain sequence is characterized by strong similarity to one of complement proteins, i.e., C1q, and shows a certain homology to the trimeric structure of factors of the TNF family, whereas a fibrous domain resembles type VIII and type X collagen (Maeda et al. 1996; Pajvani et al. 2003). Due to its structure, adiponectin can form multimers. Globular domains assemble into homotrimers, whereas fibrous domains into higher-order structures composed of 12, 18, or more adiponectin molecules (Waki et al. 2003). Adiponectin occurs in three forms which are characterized by different degree of oligomerization: a fraction with the lowest molecular weight (low molecular weight trimer-dimer, LMW) containing adiponectin trimers, a complex with medium molecular weight (middle molecular weight hexamer, MMW), and a complex with the highest molecular weight (high molecular weight multimer, 18-36-mer HMW), which is made of multimers consisting 6 (hexamer) and 12–18 adiponectin molecules, respectively (Pajvani et al. 2003; Waki et al. 2003; Kershaw and Flier 2004). Still little is known about the regulation and significance of these adiponectin complexes in serum and about the events that lead to the generation of bioactive ligand (Pajvani et al. 2003).

A basic structural unit of adiponectin being released outside of the cell is trimers composed of three protein molecules linked by hydrogen bonds within a globular domain (Nakano et al. 1996; Pajvani et al. 2003). Further oligomerization of timers can occur in blood serum, resulting in development of more complex multimer forms. Formation of disulphide bridges within fibrous domains, being formed with the participation of cysteine in codon 36 (human adiponectin) or codon 39 (murine model), is responsible for oligomerization of trimers (hexamers and higher-order multimers, HMW) (Waki et al. 2003). Furthermore, there is also a globular adiponectin in blood serum, being a product of proteolytic degradation, with leukocyte elastase – liberated by activated monocytes and/or neutrophiles – being involved in it.

Significant differences are observed in the concentration of respective adiponectin multimeric forms and their proportion in blood serum, which probably depends on such factors as gender and obesity degree (Arita et al. 1999; Table 2). Intraindividual variation in HMW fraction concentrations is of particular interest. It is believed that the HMW isoform has a pro-inflammatory effect, whereas LMW an anti-inflammatory one. The latest studies show that HMW-form adiponectin concentration is sexually differentiated (Waki et al. 2003; Horáková et al. 2015); moreover, higher levels have been found in lean subjects, whereas such relationship has not been observed for hexamers and trimers (Horáková et al. 2015; Kobayashi et al. 2004). In patients with coronary heart disease, an increased level of trimers and no changes in hexamer concentration in blood have been shown (Kobayashi et al. 2004). Body mass reduction leads to an increase in the concentration of this particular fraction of adiponectin (Kobayashi et al. 2004).

Receptors, Transport

Adiponectin bioactivity refers mostly to liver tissue, skeletal muscle tissue, and blood vessels, but bone tissue, uterus, and the brain have been only recently taken into account, too (Kharroubi et al. 2003; Kershaw and Flier 2004; Kadowaki and Yamauchi 2005; Kim et al. 2010). Adiponectin signaling pathway is not yet fully understood but it is known that adiponectin affects the target tissues by a specific membrane receptor, being found in two isoforms: AdipoR1 and AdipoR2. The specificity of adiponectin interaction with receptors and the activation of respective signaling pathways depends on the degree of its oligomerization and posttranslation modification of adiponectin (hydroxylation and subsequent glycosylation of four lysine residues and hydroxylation of seven proline residues within a collagen domain play a key role in the formation of HMW polymers, which determines adequate adiponectin bioactivity) (Kharroubi et al. 2003; Kershaw and Flier 2004). Common features and those differentiating the above isoforms of receptors for adiponectin are presented in Table 1.

Table 1 Comparative characteristics of adiponectin receptors AdipoR1 and AdipoR2

Trait	AdipoR 1	AdipoR 2	Reference
Structure	Seven transmembrane domains		Yamauchi et al. 2003
Intracellular signaling	Kinase phosphorylation: MAPK (mitogen-activated protein kinase), AMPK (AMP-activated protein kinase) Nuclear receptor PPARa activation		Yamauchi et al. 2003
Genetic loci	ADR1 – chromosome 1 (1q32.1)	ADR2 – chromosome 12 (12p13.33)	Kharroubi et al. 2003
Tissue-specific expression	Skeletal muscle Brain Heart Kidney Liver Placenta Pancreatic β cells Macrophages Osteoblasts Chondrocytes	Liver Skeletal muscle Osteoblasts Chondrocytes	Kershaw and Flier 2004; Kim et al. 2010; Kadowaki and Yamauchi 2005; Kharroubi et al. 2003; Xibillé-Friedmann et al. 2015 Berner et al. 2004 Luo et al. 2005
Binding affinity	Adiponectin trimer	Higher-order multimers (MMW, HMW)	Yamauchi et al. 2003

Metabolism

As reported in reference data, the cDNA encoding protein Acrp30 was first described by Scherer and collaborators in 1995 (Scherer et al. 1995). Adiponectin gene is located in the region of chromosome 3 (3q27) that contains the adiponectin structural gene (apM1, ACDC) (Kissebah et al. 2000; Takahashi et al. 2000; Comuzzie et al. 2001). The apM1 spans 16 kb (kilobase pairs) and is composed of three exons, being 18, 222, and 4277 kb long, respectively (Saito et al. 1999). Exon 1 does not contain an encoding sequence which occupies only a portion of exon 2 and exon 3. The genetic location of adiponectin encoding (locus 3q27) indicates its possible connection to the occurrence of many diseases, including metabolic syndrome and type 2 diabetes mellitus phenotypes (Comuzzie et al. 2001; Al-Daghri et al. 2012). Furthermore, in the promoter region of the ACDC gene, the sequences, the so-called response elements, have been found which can indicate that ACDC gene expression may change according to body energy status and lipid store of adipose tissue. Among others, these sequences are: PPAR (peroxisome proliferator-activated receptor), SREBP (sterol regulatory element-binding protein), and GR (glucocorticoid receptor), being recognized by nuclear receptors/transcription factors (Iwaki et al. 2003; Seo et al. 2004). The apM1 gene is expressed in adipose tissue only. It is characterized by an increase with the reduction of body weight under the influence of IGF-1 but drops with the development of obesity and under the influence of glucocorticoids, TNF-α, and β-adrenergic receptor agonists (Arita et al. 1999; Fasshauer et al. 2001; Fasshauer et al. 2003).

An important factor affecting the expression of ACDC gene is insulin which may inhibit the transcription of this gene or decrease the stability of mRNA, controlling at the same time adiponectin concentration in blood or accelerating its removal from bloodstream. The adiponectin-insulin interactions are, to some extent, reciprocal because adiponectin increases tissue insulin sensitivity by decreasing the concentration of triacylglyceroles in skeletal muscles, which results in enhanced insulin signaling.

The next important factor affecting the expression of apM1 gene is peroxisome proliferator-activated receptor-alpha (PPAR-α), being a dominant PPAR isoform in adipose tissue. PPAR-α's act as ligand-activated transcription factors and stimulate the expression of genes associated with carbohydrate and fatty acid metabolism (e.g., FAT/CD36, acyl-CoA oxidase, and UCP-2) and also have an effect on the proliferation and differentiation of adipocytes (Brun and Spiegelman 1997; Yamauchi et al. 2001).

One of the main functions of adiponectin is regulation of carbohydrate and fatty acid metabolism in the liver and muscles, which is directly connected with the regulation of energy balance and the magnitude of body weight. Adiponectin bioactivity depends primarily on the degree of its oligomerization which determines the specificity of its interaction with receptors, which translates into activation of respective signaling pathways (Yamauchi et al. 2003). Adiponectin receptor AdipoR1 – which shows affinity for adiponectin trimers and, by activation of the signaling pathway with the participation of the parAMPK (5′AMP-activated protein kinase), increases the uptake and oxidation of glucose and, after inactivation of

acectyl-CoA carboxylase (ACC), the oxidation of fatty acids – prevails in muscles (Yamauchi et al. 2002, 2003). The described processes take place both with globular and full-length forms of adiponectin. Additionally, in skeletal muscles, adiponectin increases the translocation of glucose transporter GLUT-4, stimulating the uptake of glucose and the production of lactic acid and inhibiting the synthesis of glycogen by myocytes (Ceddia et al. 2005).

AdipoR2 prevails in liver tissue where the regulation of glucose and fatty acid metabolism takes place mainly under the influence of adiponectin multimers (HMW). The binding of HMW with adiponectin receptor AdipoR2 activates the signaling pathway with the participation of AMPK in hepatocytes, leading to reduced activity of acetylo-CoA carboxylase and stimulation of fatty acid oxidation, and induces suppression of the molecules being involved in the process of gluconeogenesis (e.g., glucose-6-phosphatase and phosphoenolpyruvate carboxykinase) in the liver (Yamauchi et al. 2002, 2003).

The structure of adiponectin is similar to that of tumor necrosis factor alpha (*TNF-α*) and complement system; moreover, its low concentration is associated with an increase in inflammatory markers, e.g., C-reactive proteins, which suggests its involvement in the regulation of inflammation. Adiponectin concentration shows dependence on the concentration of TNF-α and the extent of inflammation, which is observed, among others, in RA (Schaffler et al. 2003; Hamman and Twardella 2006). Furthermore, adiponectin inhibits the inflammatory response by decreasing the phagocytic activity of macrophages and the production of TNF-α and inhibits the proliferation of myelomonocytic cells (Kemp et al. 2001; Shimada et al. 2004).

Adiponectin Concentration According to Anthropometric Traits

Adiponectin concentration is about 0.01% of that of all proteins being found in blood plasma. In healthy subjects, it is about 5–30 μg/ml (Arita et al. 1999). Some reference data show a positive relationship between adiponectin concentration and gender (Cnop et al. 2003); however, these are isolated reports in relation to references not presenting such a relationship (Arita et al. 1999; Table 2).

Body composition, precisely the content of fat components, shows a strong negative correlation to adiponectin concentration in blood serum. In overweight and obese subjects, a lower expression of adiponectin is observed in adipose tissue, as well as its lower concentration in blood plasma (Arita et al. 1999; Stępień et al. 2012). Among others, a negative correlation of adiponectin concentration in blood plasma to body mass index, fat mass percentage and waist to hip ratio, fasting insulinemia, and triglyceride concentration in blood serum has been demonstrated. On the other hand, a positive correlation has been observed to HDL-fraction cholesterol (Carrasco et al. 2009; De Rosa et al. 2013). There is a profound sexual dimorphism of adiponectin levels and complex distribution in serum (Pajvani et al. 2003; Alehagen et al. 2015). Adiponectin concentration is higher in women than in men (Comuzzie et al. 2001; Alehagen et al. 2015); interestingly, the demonstrated dimorphism is maintained regardless of their body composition (Cnop et al. 2003).

Table 2 Comparison of adiponectin concentration according to gender and morbid obesity or anorexia

Respondents			Age (years)	BMI [kg/m^2]	Adiponectin (μg/ml)	Reference
Differences in gender	Women, $n = 803$		–	–	8.18 ± 4.10	Comuzzie et al. (2001)
	Men, $n = 297$		–	–	7.24 ± 3.52	
	Women, $n = 106$		–	–	7.4 ± 29	Cnop et al. (2003)
	Men, $n = 76$		–	–	5.4 ± 2.3	
	Women, $n = 80$		39 ± 12	24.3 ± 5.0	4.7 ± 1.9	Tenta et al. (2010)
	Women, $n = 234$		77.0 (3.7)	27.6 ± 5.1	7884 ± 5387 pg/mL	Alehagen et al. (2015)
	Men, $n = 242$		77.0 (3.2)	26.7 ± 3.3	4829 ± 3391 pg/mL	
Obese	Hypertensive patients with simple obesity (class I), $n = 21$		52.52 ± 14.86	32.53 ± 1.71	18.18 ± 11.93	Stępień et al. (2012)
	Hypertensive patients with severe obesity (class II and III), $n = 10$		54.30 ± 12.09	38.51 ± 2.96	20.61 ± 10.26	
	Normotensive patients with simple obesity (class I), $n = 7$		46.57 ± 13.58	32.49 ± 2.18	17.81 ± 7.20	
	Control, $N = 44$		39.3 ± 14.0	23.5 ± 3.4	TAL 28.9 ± 9.4 HMW 4.4 ± 2.2	De Rosa et al. (2013)
	Obese, $N = 25$		34.9 ± 10.5	45.6 ± 9.0	TAL 8.1 ± 3.6 HMW 5.9 ± 3.7	
Bariatric operations	Morbidly obese women before/after GBP	Baseline	37.7 ± 9.6	45.0 ± 4.3	11.4 ± 4.3	Carrasco et al. (2009)
		After 6 months		32.5 ± 3.9	15.7 ± 4.8	
		After 12 months		29.5 ± 3.9	19.8 ± 6.6	
	Laparoscopic Roux-en-Y GBP	Preoperatively, $n = 33$	–	26.71 ± 0.69	1.36 ± 0.07	Shrestha et al. (2013)
		3 months postoperatively, $n = 33$	–	24.53 ± 0.62	1.60 ± 0.09 (ng/mL)	
	Morbidly obese GBP	Control groups, $n = 18$	41 (36, 47)	22 (21, 23)	3.4 (2.0, 5.3) (ng/mL)	Quercioli et al. (2013)
		Baseline, $n = 18$	43 (36, 52)	45 (43, 49)	2.6 (2.1, 3.8) (ng/mL)	
		After 12 months, $n = 18$	44 (37, 53)	31 (28, 35)	6.0 (2.2, 10.5) (ng/mL)	

Anorexia nervosa	Comparing patients with AN and BN	Control, $n = 16$		25.7 ± 2.9	20.3 ± 1.5	18.3 ± 9.8	Tagami et al. (2004)
		Obese, $n = 9$		27.0 ± 6.8	30.3 ± 5.6	5.7 ± 2.0[4] (9)	
		AN patients, $n = 31$		25.5 ± 8.1	14.0 ± 2.5	11.0 ± 7.8[2] (31)	
		BN patients, $n = 11$		23.5 ± 3.9	20.5 ± 1.8	11.5 ± 6.2[1] (11)	
	Adolescent girls with AN and healthy adolescents (0, 30, and 60 min after ingestion of OGL)	AN	0 min	–	16.7 ± 1.3	13.3 ± 6.1	Misra et al. (2007)
			30 min			12.5 ± 8.2	
			60 min			11.2 ± 5.4	
		Healthy adolescents	0 min	–	21.8 ± 3.4	11.9 ± 7.8	
			30 min			9.8 ± 2.9	
			60 min			8.7 ± 2.8	
	Comparing patients with AN and MP	Control group, $n = 38$			22.32 ± 0.40	33.24 ± 4.41	Krízová et al. (2008)
		Anorexia nervosa, $n = 28$			15.72 ± 0.36	58.44 ± 7.17	
		Obese women, $n = 77$			43.48 ± 1.12	17.02 ± 1.19	

TAL total adiponectin level, *GBP* gastric bypass surgery, *AN* anorexia nervosa, *BN* bulimia nervosa, *OGL* oral glucose load, *MP* metabolic phenotype

Adiponectin Interaction with Other Hormones/Proteins [Hormones and Proteins/Hormone Proteins]

Adiponectin gene expression (and resulting from it adiponectin concentration) is mainly dependent on body adiposity, age, and hormonal concentrations, such as estrogen, testosterone, cortisol, and FSH levels (especially in postmenopausal women) (Pajvani et al. 2003; Wang et al. 2012). There is a large variety of pathways regulating the expression and secretion of adiponectin but most papers indicate that the activity of adiponectin gene (apM1) can be reduced by TNF-α, interleukin-6, glucocorticoids, β-adrenergic agonists, catecholamines, and high testosterone, cortisol, and estrogens levels. The stimulating effects of adiponectin concentration (with even hyperadiponectinemia) can be caused by normal or low estrogen and testosterone levels, low sex hormone-binding globulin level, and high FS level (Fig. 1; Fasshauer et al. 2002, 2003; Delporte et al. 2002; Bruun et al. 2003; Lubkowska et al. 2014). Very important but still not fully clear hormone regulation of adiponectin secretion is insulin dependent. There is a variety of reports demonstrating the stimulating effects of insulin on ACRP30 gene expression or secretion (Bogan and Lodish 1999; Halleux et al. 2001). On the other hand, there is a variety of papers showing that insulin concentration can be negatively correlated to ACRP30 gene expression and resultant low adiponectin concentration (Fasshauer et al. 2002).

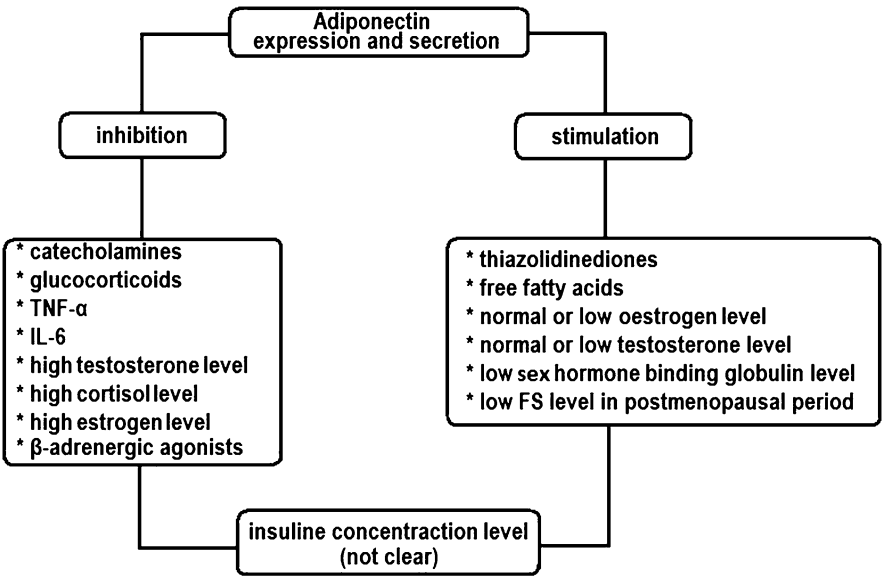

Fig. 1 Interaction of adiponectin concentration

Adiponectin Effects in Osteoporosis

Basic Information About Osteoporosis (Types, Causes, Formation Process, Consequences)

Osteoblasts and marrow adipocytes originate from a common mesenchymal progenitor. Research has shown that differentiations of bone marrow stem cells into fatty cell lines or bone cell lines are not mutually exclusive (Rosen and Klibanski 2009). Bone structure is directly dependent on the bone remodeling, an active process throughout the skeleton, being essential for calcium homeostasis and preserving the integrity of the skeleton, through the coupled activity of osteoclasts and osteoblasts (Fig. 2).

In the situation when the process of bone resorption and bone formation is dysregulated, osteoporosis is being observed with the occurrence of increased bone resorption. It is a systemic disease of the skeletal system affecting different patients at different age. It is characterized by a significantly increased likelihood of fractures due to decreased bone mineral density (BMD) and abnormal bone microarchitecture (Cummings and Black 1995).

The rate of bone resorption is greater than the rate of new bone formation; that is why a significant reduction in the weight of normal bone mass is being observed. Osteoporosis takes its greatest toll in the female population where a significant increase in incidence is observed after 50 years of age and is primarily connected with the menopause (Melton et al. 1989). Today, osteoporosis is a major public health problem, and it becomes even more serious due to the fact that the elderly population is still increasing (Van Geel et al. 2007; Kanis et al. 2007). There are many risk factors which can lead to full-blown osteoporosis but many of them are heterogeneous and not fully specific (Fig. 3).

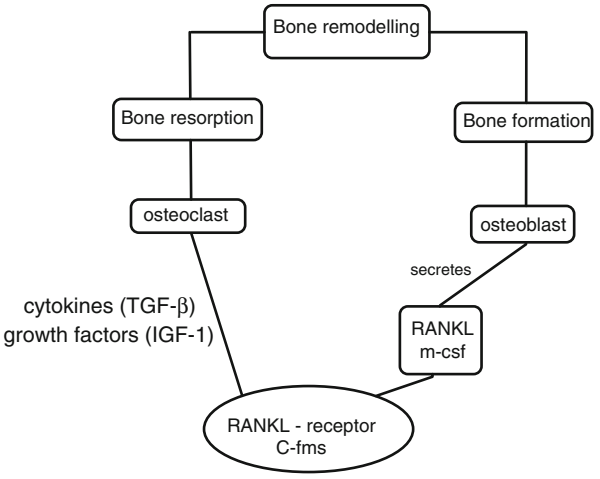

Fig. 2 Bone remodeling

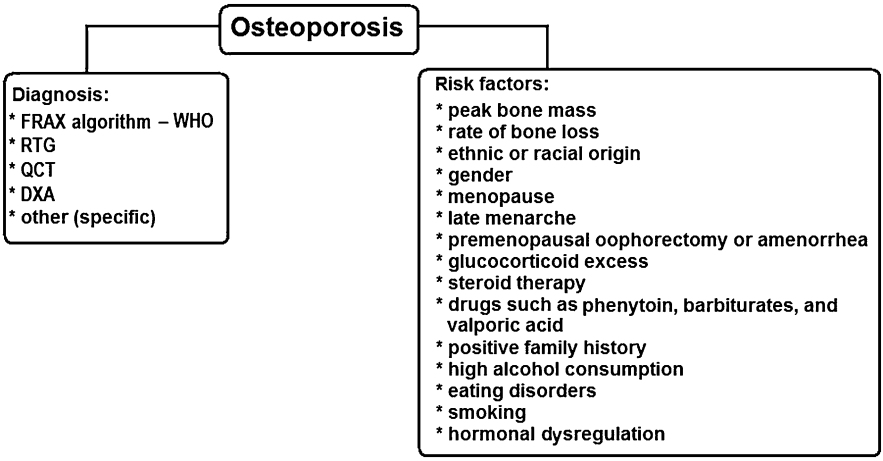

Fig. 3 Osteoporosis diagnosis and risk factors

Despite the fact that numerous papers examine this skeletal disease, some of its interactions and specific markers are still unclear. Osteoporosis is a very heterogeneous pathogenic process which depends on many causative factors. Most classifications describe osteoporosis either as primary or secondary. Primary osteoporosis is a more common form and is due to typical age-related bone loss from the skeleton. It is classified as type 1 and type 2 osteoporosis. Secondary osteoporosis results from the presence of other diseases or conditions that predispose to bone loss and is classified as type 3 osteoporosis (Ott 1998). Type 1 osteoporosis is a classic form of postmenopausal osteoporosis. Type 2 osteoporosis is being called age-related osteoporosis and affects men and women, usually after the age of 70. Secondary osteoporosis (called type 3 osteoporosis) may occur at any age; is not gender dependent; and can be caused by drugs, immobilization, or any disease (Fig. 4).

Differentiation of Osteoblasts and Adipocytes – Regulatory Factors Allowing for Adiponectin

Osteoblast Cell Differentiation

Osteoblasts are basic single nuclei bone-forming cells, differentiated from multipotent mesenchymal stem cells (Pittenger et al. 1999; Blair et al. 2008). Osteoblasts are responsible for the synthesis of cross-linked collagen and specific proteins (e.g., osteocalcin and osteopontin) which are responsible for bone matrix formation. Furthermore, osteoblasts produce a calcium and phosphate-based mineral, hydroxyapatite, that can be deposited into the organic matrix forming a specific and mineralized bone tissue (mineralized matrix) (Blair et al. 2011). These specific features of osteoblast-lineage cells make them occupy a central position in bone metabolism and structure. Of course, the formation of a structurally sound skeleton,

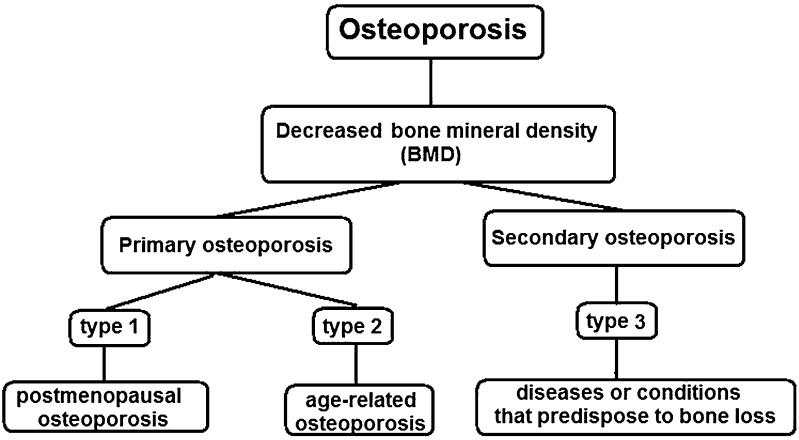

Fig. 4 Primary and secondary osteoporosis

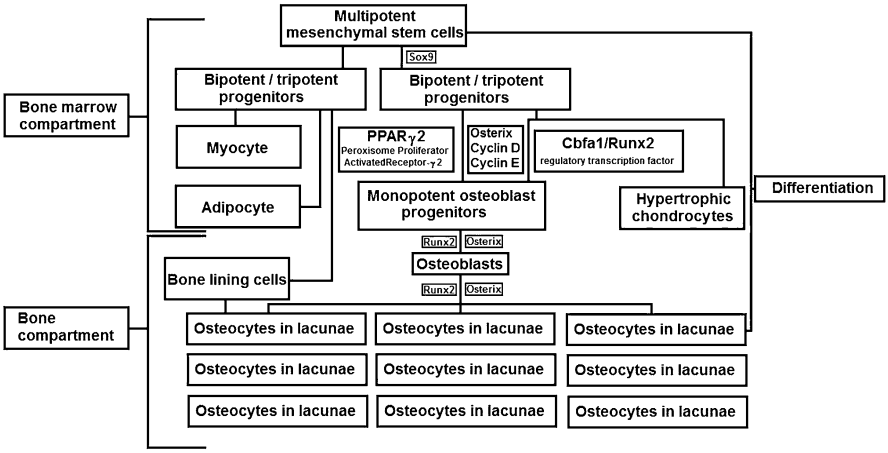

Fig. 5 Cell differentiation in the mesenchymal system

with its strength and integrity conserved by constant remodeling, and the formation as well as activation of the major bone-resorbing cell, the osteoclast, are the result of direct and indirect influences of osteoblasts. Osteocytes derive from osteoblasts and are formed by the incorporation of osteoblasts into the bone matrix (Fig. 5). Osteocytes remain in contact with each other and with cells on the bone surface via gap junction coupling of cells passing through the matrix via small channels, the canaliculi, that connect the cell body – containing lacunae – with each other and with the outside world (Aarden et al. 1994).

The membrane that covers the outer surface of all bones, except at the joints of long bones, called periosteum, contains a large number of multipotent mesenchymal stem cells. During cell differentiation, they give rise to osteoblasts (similar pathway

is mesenchymal steam cells in bone matrix). This process is being controlled under the expression of regulatory transcription factor Cbfa1/Runx2, the activity of which can also be found in hypertrophic chondrocytes. Furthermore, osteoblast differentiation is under control of osterix (Karsenty 2008; Zhu et al. 2012). Osterix regulates the expression of a set of ECM proteins which are involved in terminal osteoblast differentiation and is associated with bone mineral density.

The most important group of growth factors responsible for the skeletal differentiation and bone formation is a group of bone morphogenetic proteins (BMPs), also known as cytokines, metabologens or cartilage-derived morphogenetic proteins (CDMPs), or growth differentiation factors (GDFs).

A large group of BMPs family belongs to the transforming growth factor beta (TGF-β) superfamily of proteins, whereas the rest is being classified as a metalloproteinase. The total number of BMPs is 20, but in last few years this number has changed. Their mechanism is based on specific interaction with bone morphogenetic protein receptors (BMPRs). Activation of the signaling pathways of BMPRs results in members of the SMAD protein family reaction (Bleuming et al. 2007). The most important for osteoblast differentiation and bone formation are the BMP2 (most important), BMP3, BMP4, BMP7, and BMP8a genes. Any mutations that may occur in the BMPs genes may lead to human disorders which affect the skeleton. The SMAD intracellular protein family is proteins that are responsible for the transduction of extracellular signals into the nucleus where they activate downstream gene transcription (Park and Morasso 2002).

Other growth factors being relatively important in the skeletal differentiation and bone formation is the transforming growth factor beta (TGF-β) family which belongs to the same transforming growth factor beta superfamily as BMPs and possess similar signaling elements in the TGF-beta signaling pathway. Furthermore, the multifunctional fibroblast growth factor family (FGFs), which is formed by 22 growth factors and has a great variety of effects, is essential for the bone formation and regulation. Mostly, the family of fibroblast growth factors (FGFs) determines where skeletal elements occur in relation to the skin (Olsen et al. 2003; Moore et al. 2005).

Multipotent mesenchymal stem cells are the site of origin not only for chondrocytes and osteoblasts but also for myocytes and marrow adipocytes (Rosen and Klibanski 2009). The phenotype of cells depends on diverse ligands of PPARγ2 (peroxisome proliferator-activated receptor-γ2). The activation of PPARγ2 is responsible for regulation of different pathways which may lead to full or partial expression of the adipocyte phenotype cell, suppression of osteoblast differentiation, or both. This correlation is very important for the correct understanding of skeletal system metabolism, as there is evidence that marrow fat increases with age in humans in which osteoblast production is observed (Rosen and Klibanski 2009). Normally, bone remodeling is being observed during the lifetime but bone loss increases with aging, both in males and females. This process occurs due to a reciprocal increase in adipocyte development and a decrease in osteoblast differentiation. Adiponectin is being produced by differentiated adipocytes and changes in its concentration have been observed in many different phases of life. It seems

essential for osteoblastogenesis that adiponectin and its receptors (AdipoR1 and AdipoR2) are present in bone-forming cells, and their origin is the same – multipotent mesenchymal stem cells (Berner et al. 2004; Shinoda et al. 2006). Reports indicate a potential effect of adiponectin on bone tissue remodeling, due to induction of osteoblasts proliferation and differentiation. Human osteoblasts show the expression of both adiponectin receptors and adiponectin. Adiponectin stimulates human osteoblast proliferation and differentiation (proliferation activity via the AdipoR/JNK pathway, differentiation activity via the AdipoR/p38 MAPK pathway), as it increases the expression of alkaline phosphatase (due to the adiponectin receptor subtype AdipoR1 activity), osteocalcin, whereas type I collagen is correlated with bone density mineralization (Fig. 6; Kanazawa et al. 2007; Mitsui et al. 2011).

This conclusion fully indicates that osteoblastic proliferation and differentiation activity takes place through AdipoR1, and high adiponectin levels enhance bone mineral density and osteoblast differentiation (Luo et al. 2005).

Influence of Adiponectin on Chondrogenesis and Osteblastogenesis

The RANK-RANKL (*receptor activator of nuclear factor kappa-B* and *receptor activator of nuclear factor kappa-B ligand*) system is responsible for normal bone tissue homeostasis. RANKL has an activating effect on osteoclasts, stimulating bone resorption (osteoclastogenesis), whereas osteoprotegerin (OPG protein) neutralizes the effect of RANKL, inhibiting this process (Inage et al. 2015). Some studies suggest the further data analysis adjusting for potential confounders to reveal that the OPG/RANKL ratio is positively associated with adiponectin (Tenta et al. 2010). Excessive activation of RANKL may lead to osteoporosis, e.g., periarticular osteoporosis, as is the case of RA (rheumatoid arthritis) (Inage et al. 2015). Little is known about the influence of adiponectin on chondrogenesis processes. It has been observed that in diseases with disturbed homeostasis of this process an increased adiponectin concentration is seen; moreover, chondrocytes show the expression of both AdipoR1 and AdipoR2 (Xibillé-Friedmann et al. 2015). Some references have proven a pro-inflammatory effect of adiponectin on chondrocytes which, by inducing the expression of nitric oxide synthase 2 (NOS2), stimulates the release of interleukin 6 (IL-6), matrix metalloproteinases (MMP-3, MMP-9), and chemokine MCP-1 (*monocyte chemotactic protein*) (Lago et al. 2008; Sun et al. 2015). This is confirmed by studies on an animal model which demonstrated that adiponectin exacerbates collagen-induced arthritis via enhancing Th17 response and prompting RANKL expression. Adiponectin injection resulted in an earlier onset of arthritis, an aggravated arthritic progression, more severe synovial hyperplasia, bone erosion, and osteoporosis in CIA mice (Sun et al. 2015). There have been also reports demonstrating the stimulating effect of adiponectin on chondrocyte differentiation and proliferation (Frommer et al. 2010). Furthermore, some references indicate the anti-inflammatory antiadhesive effect of adiponectin (Challa et al. 2010).

As regards osteogenesis, many studies suggest a functional role of adiponectin in bone homeostasis. The effect of adiponectin on bone tissue may be direct, by

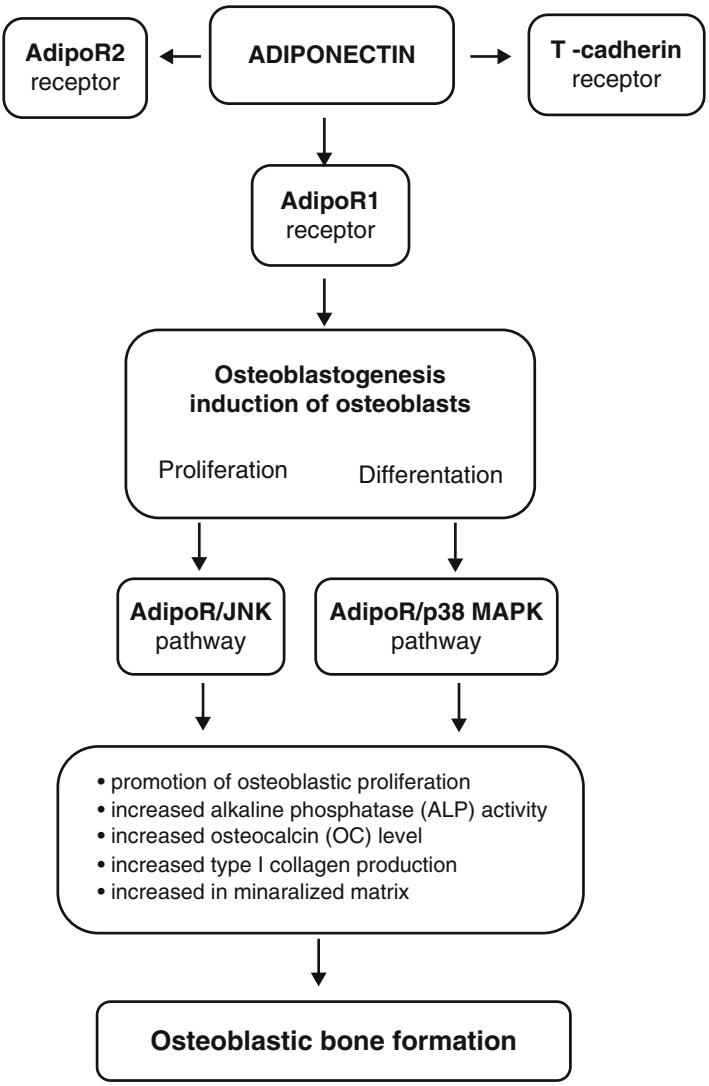

Fig. 6 Adiponectin correlation with bone mineral density

influencing osteoblasts, and indirect, by affecting osteoclasts. Adiponectin can increase bone mass by increasing the expression of alkaline phosphatase, osteocalcin, and type 1 collagen, stimulating human osteoblast proliferation and differentiation (Luo et al. 2005). Additionally, the inhibitory effect of adiponectin on differentiation of osteoclasts from CD14+ monocytes and inhibition of osteoclast resorption activity also contributes to increased bone mass (Oshima et al. 2005). Both in human and animal models, the mitogenic effect of adiponectin on osteoblasts and the inhibitory one on osteoclast proliferation have been demonstrated

independently of the RANK/RANKL/OPG system (Williams et al. 2009). More importantly, adiponectin influence can be observed at the level of mesenchymal cells, stimulating their differentiation towards osteoblasts, increasing the expression of osteoblastogenesis markers (Runx2, BMP-2). In addition, the protective effect of adiponectin on bone tissue may also result from its anti-inflammatory action, which is induced by inhibition of TNF-α-mediated NFkB activation, thus reducing the activity of osteoclasts via the RANK/RANKL/OPG pathway (Khosla 2001; Lee et al. 2009).

It would seem that the above data clearly indicate a positive effect of adiponectin on bone remodeling, but there are also references in literature showing the stimulating effect of adiponectin on osteoclastogenesis by enhancing the RANKL expression and down-regulating the expression of osteoprotegerin (OPG) (Luo et al. 2006). Consistent with this finding, culture of osteoblasts with adipocyte-conditioned media was reported to decrease the osteoblastogenic transcription factor Runx2 expression, an effect that was abrogated by knockdown of AdipoR1 (Liu et al. 2010). The index of bone mineral density (BMD) reflects to some extent the direction of bone turnover. The data referring to the effect of adiponectin on BMD are largely contradictory. There is no sufficient evidence to clearly conclude negative correlation between adiponectin concentration in blood serum and BMD but most references, nevertheless, report such a relationship (Krízová et al. 2008; Singhal et al. 2014).

Factors Affecting Bone Mass and Regulating Bone Remodeling Allowing for Adiponectin; Adiponectin Receptors Associated with Bone Metabolism

The bone remodeling cycle maintains skeletal integrity through balanced activities of its constituent cell types. It is an active and dynamic lifelong process where mature bone tissue is removed from the skeleton (bone resorption) and new bone tissue is formed (bone formation). In bone remodeling, three different cell types are involved: osteoblasts, osteocytes, and osteoclasts.

Bone-forming osteoblasts are mainly engaged in bone formation. They are specific single nuclei bone-forming cells, differentiated from multipotent mesenchymal stem cells. Their main role is to produce organic bone matrix and aid its mineralization (Pittenger et al. 1999; Blair et al. 2008; Karsenty et al. 2009).

Very important in the regulation of bone mass are osteoclasts. It is one of the types of bone cells responsible for resorption of bone tissue. This is an essential process in the maintenance, repair, and remodeling of bones of the vertebral skeleton. Osteoclasts dismount mineral bone structure in the process of bone resorption at a molecular level by acidic and enzymatic degradation of extracellular matrix (ECM) proteins through collagenase secretion (using hydrolytic enzymes, such as members of the cathepsin and matrix metalloproteinase (MMP) groups). Significant for the activity of osteoclasts being expressed by them is one of the collagenolytic, papain-like, cysteine proteases called cathepsin K. It is synthesized as a proenzyme

and activated by autocatalytic cleavage to its mature active form that is being secreted into the resorptive pit and is involved in the degradation of type I collagen and other noncollagenous proteins (Yasuda et al. 1998; Teitelbaum 2000, 2007; Teitelbaum and Ross 2003; Fuller et al. 2006).

Equally important for the enzymatic activity of osteoclasts are matrix metalloproteinases (MMPs), especially MMP-9, MMP-10, MMP-12, and MMP-14. The activity of only one of these metalloproteinases has been identified. Except MMP-9, little is known about their relevance to osteoclasts but summing up the activity of MMP-9 it can be easily noticed that it is associated with the bone microenvironment and is known to be required for osteoclast migration and as powerful gelatinase (Teitelbaum 2000, 2007).

Simultaneous and proportional activity of osteoclasts and osteoblasts is essential in bone tissue regulation and function (Pittenger et al. 1999; Teitelbaum 2007; Blair et al. 2011).

Equally important is the third group of bone cells derived from osteoprogenitors called osteocytes. They are very common cells in mature bone, reside inside lacunae and canaliculi, and, comparing to all other bone cells, their life span is very long.

During the growth of osteoblasts, they may be trapped inside the matrix that they secrete and, after transformation, they become osteocytes. Osteocytes are connected to each other through long cytoplasmic extensions. Comparing to osteoclasts and osteoblast, they are capable of molecular synthesis and modification, as well as transmission of signals.

Osteocytes are capable of producing nerve growth factors after bone fracture (due to glutamate transporters). Most papers indicate that osteocytes are thought to be mechanosensory cells that control the activity of osteoblasts and osteoclasts. Furthermore, they produce osteocyte specific proteins such as sclerostin (regulates mineral metabolism), PHEX, DMP-1, MEPE, and FGF-23 (regulates phosphate and biomineralization) (Bonewald 2011).

Potential Applications to Prognosis, Other Diseases or Conditions

Osteoporosis in Different Conditions Associated with Decreased or Increased Adiponectin Levels

One of the potential markers of **perimenopausal osteoporosis** can be adiponectin. It is believed that the main role in the mechanism of bone metabolism in the perimenopausal period is played by estrogens and androgens, especially DHEA (dehydroepiandrosteron) (Rosen and Bouxsein 2006; Ağbaht et al. 2009). However, from among the hormones being secreted by adipose tissue, particular importance is attached to the role of leptin and adiponectin as significant protective and preventive, respectively, mediators of osteoporosis (Rosen and Bouxsein 2006; Jürimäe and Jürimäe 2007; Ağbaht et al. 2009; Zillikens et al. 2010). It has been shown that adiponectin levels are considerably higher in postmenopausal women compared to premenopausal ones (Table 3). It should be noted that adiponectin receptors

Table 3 Comparison of adiponectin concentration in perimenopausal women

Respondents		Age (years)	BMI [kg/m^2]	Adiponectin (μg/ml)	Reference
Total (pre- and postmenopausal)	Adult women, $n = 1467$	47.7 ± 14.2	26.4 ± 4.7	12.3 ± 5.8	Zillikens et al. (2010)
	Adult men, $n = 1164$	48.6 ± 14.0	27.1 ± 3.9	8.0 ± 4.1	
	Adult, $n = 153$	57.8 ± 13.7	27.6 ± 2.4	12.2 ± 6.3	Jürimäe (2007) [158]
	Adult, $n = 1735$	50.0 ± 13.0	25.5 ± 4.7	8.3 (3.9)	Richards et al. (2007)
Premenopausal	Adult, $n = 98$	45.2 ± 4.3	29.9 ± 6.2	12.0 ± 4.7	Jürimäe and Jürimäe (2007)
	Middle-aged, $n = 42$	40.8 ± 5.7	25.9 ± 2.8	8.4 ± 3.2	
	Adult, $n = 25$	47.80 ± 3.14	30.01 ± 5.22	7.9 ± 5.81	Kontogianni et al. (2004)
	Adolescents, $n = 105$	15.4 ± 1.9	23.1 ± 4.0	30.79 ± 14.48	Huang et al. (2004)
Postmenopausal nondiabetic (with hip fracture), $n = 105$	Nonosteoporosis	58.4 ± 8.2	31.2 ± 5.9	6.33 ± 0.51	Özkurt et al. (2009)
	Osteoporosis	68.4 ± 8.0	25.5 ± 9.9	6.99 ± 0.5	
	Total	63.4 ± 8.1	28.5 ± 7.9	6.66 ± 0.45	
Postmenopausal	$n = 55$	54.47 ± 5.36	28.89 ± 4.19	11.94 ± 7.00	Kontogianni et al. (2004)
	$n = 84$	52.5	29.4	13.25	Ağbaht et al. (2009)
	Women, $n = 447$	76.0 ± 8.4	24.4 ± 3.8	16.28 ± 7.1	Araneta et al. (2009)
	Men, $n = 484$	74.8 ± 8.3	25.8 ± 3.2	11.1 ± 5.8	
	Control, $n = 16$	70.2 ± 1.0	27.4 ± 0.8	Peripheral plasma 12549 ± 1530 ng/m Bone marrow plasma 8939 ± 1484 ng/m	Mödder et al. (2011)
	Estrogen treated, $n = 16$	72.9 ± 1.7	28.6 ± 1.4	Peripheral plasma 12919 ± 1544 ng/m Bone marrow plasma 9615 ± 1268 ng/m	

AdipoR1 and AdipoR2 have been found in uterus, which may suggest the effect of adiponectin on the endometrium, and is involved in regulation of gonadotropin secretion (Palin et al. 2012). The role of adipose tissue in female reproductive system homeostasis is additionally emphasized by the fact that obese women go through puberty earlier and are predisposed to polycystic ovary syndrome (PCOS), whereas underweight in women is associated with later sexual maturation and a risk of premature delivery (Jürimäe and Jürimäe 2007). It is suggested that adiponectin negatively correlates with the levels of free testosterone, DHEA-S (dehydroepiandrosterone sulfate), and estradiol and positively with SHBG (*sex hormone binding globulin*) in postmenopausal women (Siemińska et al. 2006; Matsui et al. 2012). Some studies suggest that possible regulation of human osteoprogenitor cells by estrogen indicate – which is in line with previous murine studies – that estrogen suppresses the proliferation of human bone marrow lin-/Stro1+ cells, which likely represent early osteoprogenitor cells (Mödder et al. 2011). In the light of the latest data, adiponectin effects may be accomplished by modification of OPG and/or RANKL expression in osteoblasts and bone marrow stromal cells (Rosen and Bouxsein 2006). In human osteoblasts, the effect of 17β-estradiol (E2) on adiponectin and regulation of OPG and RANKL expression has been observed. Through blocking the activation of adiponectin-induced p38 MAPK, E2 suppressed adiponectin-regulated OPG/RANKL expression and then inhibited osteoclastogenesis (Wang et al. 2012). As regards the above described findings, it seems that new hormonal markers, including adiponectin, may be useful in the prediction of bone loss and risk of fractures in osteoporosis in postmenopausal women (Özkurt et al. 2009; Araneta et al. 2009).

In rheumatoid arthritis (RA), osteoporosis – localized or generalized – is secondary as a consequence of inflammatory lesions. In patients with RA, significantly higher adiponectin concentration in blood serum was observed compared to healthy subjects (Lago et al. 2006). Moreover, adiponectin concentration in synovial membrane was higher in RA patients than in those with OA (osteoarthritis) (Otero et al. 2006; Schaffler et al. 2003; Table 4). In view of the adiponectin effects in chondrogenesis and osteogenesis being described above, it can be a potential marker of osteoporosis in inflammatory diseases, such as RA or osteoarthritis. As mentioned before, TNF-α correlates with adiponectin concentration and inflammatory response; moreover, in vitro studies revealed that adiponectin may also have a pro-inflammatory effect which is associated with TNF-α activity (Schaffler et al. 2003). It is therefore considered that pro-inflammatory effects in synovial membrane, being induced by adiponectin, are probably mediated by TNF-α (Herfaarth et al. 2006). It could be suggested that serum adiponectin level is a simple useful biomarker associated with early radiographic disease progression in RA, independent of RA-confounding factors and metabolic status (Otero et al. 2006; Giles et al. 2011; Meyer et al. 2013).

Obesity is characterized by increased body weight and excess adipose tissue. Reference studies have shown that indices of body adiposity, e.g., BMI (*body mass index*) and FM (*fat mass*), negatively correlate with adiponectin concentration and positively with bone mineral density (BMD) (Arita et al. 1999; Stefan et al. 2002; Misra et al. 2007; Carrasco et al. 2009). As is well known, bone loss can lead to

Table 4 Comparison of adiponectin concentration in patients with rheumatoid arthritis

Respondents		Age (years)	BMI [kg/m^2]	Adiponectin (μg/ml)	Reference
Controls	Women, $n = 124$	57.5 ± 16.6	52.8 ± 7.0	3.6	Lago et al. (2006)
	Men, $n = 22$	45.6 ± 13.8	22.3 ± 2.8	2.3	
RA	Women, $n = 110$	59 ± 14	22.2 ± 3.8	10.1	
	Men, $n = 31$	61.0 ± 12.7	23.2 ± 3.2	2.6	
Controls, $n = 18$	Women, $n = 10$ Men, $n = 8$	48.3 ± 16.1	24.36 ± 0.83	7.6 ± 0.7 μg/mL	Otero et al. (2006)
RA, $n = 31$	Women, $n = 22$ Men, $n = 9$	46.1 ± 14.1	25.88 ± 0.63	13.56 ± 2.1 μg/ml	
RA	$n = 152$	59 ± 8	28.1 ± 5.0	32 (20–43) mg/L	Giles et al. (2011)
UA	$n = 159$	47.2 ± 13.8	24.7 ± 4.6	4.9 ± 3.4 (μg/ml)	Meyer et al. (2013)
ERA	$n = 632$	48.5 ± 12.2	25.2 ± 4.6	5.0 ± 3.7 (μg/ml)	

RA rheumatoid arthritis, *UA* undifferentiated arthritis, *ERA* early rheumatoid arthritis

osteopenia or osteoporosis and therefore it is quite popularly believed that high BMI protects from osteoporosis. Bariatric surgery is an option for morbid obesity treatment but has a negative effect on bone tissue metabolism. Regardless of the type of surgical intervention (VBG – vertical banded gastroplasty, LAGB – laparoscopic adjustable gastric band, RYGB – Roux-en-Y gastric bypass), they reduce the volume of orally ingested food. It should be noted that, apart from intended reduction of fat mass, they induce at the same time a loss in bone mass, increasing the risk of osteoporotic fractures. The reason for secondary osteoporosis may be, quite typical after bariatric surgeries, the occurrence of malabsorption syndrome, particularly of vitamins D and K as well as vitamin B12, Ca ions, and folic acid (Decker et al. 2007; Mahdy et al. 2008; Carrasco et al. 2014). Furthermore, a decrease in leptin concentration and increase in adiponectin concentration in blood serum are observed in these patients, probably as a consequence of weight loss, which can induce the activation of response pathway towards bone loss by affecting the RANK/RANKL/OPG pathway (Carrasco et al. 2009; Shrestha et al. 2013; Quercioli et al. 2013). As regards postbariatric patients, it seems that it is not the specific adiponectin level but a sudden increase of its concentration that may be a signal activating the changes towards bone loss (Table 2).

Anorexia (anorexia nervosa, AN) is a type of psychosomatic disorder which leads to lipoatrophy and weight loss and deterioration of bone tissue quality, the consequence of which is osteoporosis and increased risk of low-energy bone

fractures (Ohwada et al. 2007). The background of secondary osteoporosis in AN is hormonal disorders, including hypoestrogenism, hypoandrogenism, and hypercortisolemia (Ohwada et al. 2007). Hormonal disorders also refer to decreased IGF-1 concentration and increased growth hormone, ghrelin, and peptide Y concentrations. A consequence of the above disorders is a decreased value of peak bone mass which, as is well known, is essential for attenuation of bone loss progressing with age, especially following the menopause. In the formation of osteoporotic lesions, the lack of many vitamins and mineral compounds being normally contained in food (e.g., vitamin D, calcium, phosphorus) is also of importance. Furthermore, it is believed that increased bone resorption being induced by a decrease in the concentration of 17-beta-estradiol in blood serum of patients, which in turn induces reduced osteoprotegerin and increased osteoclast activation, is crucial for the development of osteoporosis in AN (Ostrowska et al. 2010). As regards AN patients, most references report high adiponectin values (Krízová et al. 2008; Misra et al. 2007) but not all results are conclusive (Tagami et al. 2004). Nevertheless, the levels of adiponectin concentration in AN subjects are always higher than in obese ones, which is associated with the inverse relationship of insulin levels, which significantly decrease in anorexia and increase in obesity (Tagami et al. 2004; Krízová et al. 2008; Shrestha et al. 2013; Quercioli et al. 2013). The reason for increased adiponectin concentration with weight loss is not known; nevertheless, it can be associated with the compensation mechanism of glucose metabolism reduction (Pannacciulli et al. 2003). Additionally, adiponectin as a potential marker of osteoporosis is also negatively correlated with BMD which is significantly reduced in patients with anorexia (Misra et al. 2007; Krízová et al. 2008; Singhal et al. 2014), which suggests that the increased bone resorption in AN mentioned before can be activated by an increase in adiponectin concentration being induced by reduced amount of adipose tissue which, as a further consequence, interferes with the RANK/RANKL/OPG system and shifts bone metabolism towards excessive activation of osteoclasts (Misra et al. 2007). It should be noted, however, that OPG and expression of RANKL are regulated by many factors, among others by estrogens, while hypoestrogenism induces a decrease in OPG and an increase in RANKL (Khosla et al. 2002). AN is associated with hypogonadism, therefore decreased OPG values could be expected (Khosla et al. 2002). It turns out, however, that OPG concentration in these subjects is increased, which can be associated with the hypothesis of compensation mechanism, being activated in response to low BMD which, for reasons that are not fully known, does not increase bone mass (Misra et al. 2003; Table 2).

In patients with **type 1 diabetes**, an increased adiponectin concentration is observed, while in those with type 2 diabetes, a decreased one, compared to healthy subjects (Retnakaran et al. 2010; Pala et al. 2015; Ljubic et al. 2015; Horáková et al. 2015; Table 5). Increased adiponectin concentration in patients with type 1 diabetes may be associated with reduced bone mineral density and induce diabetic osteopenia. Other causes of diabetic osteopenia are probably: insulin deficiency being characterized, among others, by anabolic effect on bone tissue (Hofbauer et al. 2007; Vestergaard 2007), accumulation of nonenzymatic protein glycosylation

Table 5 Comparison of adiponectin concentration in diabetes mellitus

Respondents			Age (years)	BMI [kg/m^2]	Adiponectin (μg/ml)	Reference
Comparing women with NTG, GIGT and defined by exceeding 2 or more NDDG glycemic thresholds (GDM)	NGT, $n = 259$	In pregnancy	33.9 ± 4.3	23.1 [21.3–26.9] +11.4 [8.6–14.5] kg	8.0 [6.2–10.0]	Retnakaran et al. (2009)
		At 3 months postpartum			8.6 [6.6–10.6]	
	GIGT, $n = 91$	In pregnancy	34.2 ± 4.2	23.5 [21.8–277] + 10.0 [7.3–145] kg	7.0 [5.2–8.7]	
		At 3 months postpartum			7.6 [5.4–9.9]	
	GDM, $n = 137$	In pregnancy	34.5 ± 4.3	25.0 [22.0–30.1] + 9.1 [5.9–12.7] kg	7.0 [5.3–8.5	
		At 3 months postpartum			8.2 [6.1–10.4]	
Comparing women with GDM and without glucose intolerance	Women with GDM, $n = 40$		–	–	At delivery 3.92 ± 4.65	Pala et al. (2015)
			–	–	In umbilical cord 20.77 ± 12.04	
			–	–	Postpartum 11.81 ± 5.81	
	Control, $n = 40$		–	–	At delivery 6.7 ± 6.49	
			–	–	In umbilical cord 27.78 ± 9.29	
			–	–	Postpartum 7.8 ± 5.97	

(*continued*)

Table 5 (continued)

Respondents			Age (years)	BMI [kg/m^2]	Adiponectin (μg/ml)	Reference
T1DM **Most (97%) were white and half were male**	1-year examination, $n = 184$		–	19.5 (3.5)	11.9	Le Caire and Palta (2015)
	4-year examination, $n = 231$		–	21.3 (4.2)	11.4	
	7-year examination, $n = 137$		–	22.8 (4.3)	11.3	
	9-year examination, $n = 187$		–	25.2 (5.0)	10.2	
	20-year examination, $n = 304$		–	28.3 (5.9)	10.2	
Diabetic nephropathy	T1DM, $n = 87$		–	–	15.37	Ljubic et al. (2015)
	T2DM, $n = 132$		–	–	8.07	
Comparing patients with and without T2DM	Control groups, $n = 269$	Women, $n = 143$	56.8	25.3 ± 1.4	TAL = 10.34; HMW = 4.71	Horáková et al. (2015)
		Men, $n = 126$	55.8	26.7 ± 3.5	TAL = 8.04; HMW = 4.46	
	T2DM, $n = 282$	Women, $n = 164$	62.1 ± 9.2	32.03 ± 5.9	TAL = 5.32; HMW = 2.92	
		Men, $n = 118$	63.9 ± 8.7	31.84 ± 5.2	TAL = 5.12; HMW = 3.03	

T1DM type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *GDM* gestational diabetes mellitus, *NTG* normal glucose tolerance, *GIGT* gestational impaired glucose tolerance, *TAL* total adiponectin level

(glycation) end-products in bone matrix (Vestergaard 2007), and deficiency of insulin-like growth factors (IGF-1, IGF-2) (Vestergaard 2007). So far, the pathogenesis of diabetic osteopenia has not been explained, or whether it represents a late complication of type 1 diabetes or a comorbid condition. Nevertheless, it is characterized by a higher rate of bone fractures than type 2 diabetes or hyperadiponectinemia (Hofbauer et al. 2007; Ljubic et al. 2015).

It was believed in the past that **type 2 diabetes** (T2DM, diabetes mellitus type 2) does not predispose to osteoporosis, which results from the fact that BMD in these subjects is mostly normal or even raised (Siddapur et al. 2015). This is probably a result of overweight and obesity which is often associated with type 2 diabetes and determines greater skeletal loading (Hofbauer et al. 2007). Furthermore, hyperinsulinemia, occurring in prediabetes and early DM2, reduces the production of sex hormone binding globulin (SHBG) and, consequently, increases free estradiol level in blood serum, which seems to be important in postmenopausal women (Siddapur et al. 2015). Reduced adiponectin concentration being observed in type 2 diabetes can also be of significant antiosteoporotic importance, as evidenced by the effect of adiponectin on the bone remodeling mentioned before (Ouchi et al. 2000; Williams et al. 2009; Ljubic et al. 2015; Horáková et al. 2015). Nevertheless, despite high densitometric values in patients with type diabetes, there is a high risk of fractures, which is evidenced by population studies (Janghorbani et al. 2007). This inconsistency results from the fact that bone densitometry is not able to provide complete information about the quality of bone, which consists of: its microarchitecture, rate of bone remodeling, accumulation of bone microdamages leading to microfractures, and degree of matrix mineralization. Unfortunately, modern medicine – despite its great development – does not yet have a tool which would be able to determine these traits intravitally. A probable cause of the increased risk of fractures in type 2 diabetes is the reduced number of osteoblasts and delayed formation of osteoid and its mineralization, but determination of its causes still remains an open question (Clowes et al. 2002). Moreover, a reduced concentration of adiponectin has been found in pregnant women, in whom hypoadiponectinemia in pregnancy predicts postpartum insulin resistance, beta-cell dysfunction, and fasting glycemia (Retnakaran et al. 2010; Pala et al. 2015). Researchers found that adiponectin concentrations in the circulation of GDM (gestational diabetes mellitus) patients are regulated by changes in glucose and insulin metabolism (Pala et al. 2015). Therefore, they suggest that adiponectin concentration may be relevant to the pathophysiology relating GDM with type 2 diabetes (Retnakaran et al. 2010).

Summary Points

1. Adiponectin is one of the hormones of adipose tissue which seems to link its metabolism with the metabolism of bone tissue, which is confirmed to some extent by the presence of adiponectin receptors AdipoR1 and AdipoR2 in human osteoblasts.

2. Despite still much controversy, it seems that changes in the adiponectin signaling can be associated with diseases of cartilaginous and bone tissues.
3. A number of clinical studies have shown a negative correlation of adiponectin with BMD and a positive one with biochemical markers of bone loss; moreover, in majority of in vitro studies, the stimulating effect of adiponectin on osteoblast differentiation and mineralization, as well as on osteocalcin expression, has been found.
4. It is postulated that adequate increase in adiponectin concentration affects bone loss, which may be associated with the modulation of inflammatory condition and RANK/RANKL/OPG signaling pathway.
5. Adiponectin is a noteworthy hormone of adipose tissue of potential importance as a marker of osteoporosis, both perimenopausal osteoporosis and that secondary appearing in different medical conditions associated with inflammation or weight loss.

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