ADIPOCYTOKINES IN BLOOD PRESSURE VARIATIONS AND HYPERTENSION: AN OVERVIEW

Abdulhalim Salim Serafi

Department of Physiology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
Email: abdulhalims@hotmail.com

ABSTRACT

In view of diverse reports providing positive or negative role of adipocytokines in the progression of blood pressure leading to prehypertension and hypertension, and some of the controversial results, we planned to carry out comprehensive review of literature for understanding the role of some of the adipokines (adiponectin, leptin, resistin and apelin). Adipocytokines have cardioprotective properties in cardiovascular risk and disease. Higher leptin value is an independent predictor of peripheral artery disease in hypertensive patients . Hyperleptinemia is involved in endothelial dysfunction especially in hypertensive obese patients. Leptin levels were found to be higher in patients with uncontrolled hypertension compared to those with controlled hypertension, and hyperleptinemia was revealed as a predictor for arterial stiffness in hypertension patients. Some of the recent studies reveal adiponectin in obesity in relation to blood pressure, protection of incident hypertension by adiponectin independent of body fat, association of adiponectin with arteriolar vessel caliber in hypertensive subjects and hypertension associated with adiponectin polymorphism. Information provided in the current review indicates that further studies be conducted to understand the role and regulation of adipocytokines mainly in normal healthy people, people having blood pressure variations, and people with hypertension.

Key words: adipocytokines, blood pressure variations, hypertension, leptin, adiponectin.

INTRODUCTION

Studies present positive as well as negative effect of adipokines in initiating the dysfunctions leading/ progressing to high-normal blood pressure, prehypertension and hypertension. A prestigious Saudi prize - 'King Faisal International Prize' was awarded on the recognition of research on leptin (KFF – KFIP – Winners, 2013). There are various phenotypes (Modolo *et al.,* 2014) and approaches and mechanisms for explaining the occurrence of hypertension (Trott and Harrison, 2014; Vaněčková *et al.,* 2014; Serafi *et al.,* 2016). Literature shows that much clinical and basic research has been conducted but the intricate etiology of hypertension is yet not known (Vaněčková *et al.,* 2014). Hence, it seems quite significant approach to carry out a comprehensive study on apparently healthy young population and to clarify the role of prehypertension progressing to hypertension as has been suggested previously (Viera, 2011).

There is a long list of factors that can be assessed/ determined to reach partly to certain conclusion for understanding the role of those factor in the occurrence of hypertension and the management of hypertension and other cardiovascular disorders. We in the current review are interested to clarify the role of some important adipokines as been pointed out recently (Trott and Harrison, 2014; Blüher and Mantzoros, 2015; Xia *et al.,* 2015; Bell and Rahmouni, 2016; Tsai *et al.,* 2016; Dutheil *et al.,* 2017; Jedzura *et al.,* 2017; July *et al.,* 2017; Lau *et al.,* 2017).

Adipocytokines have cardioprotective properties in cardiovascular risk and disease (Dutheil *et al.,* 2017; Lau *et al.,* 2017). Several studies show the role of adipokines in children with primary arterial hypertension (Jedzura *et al.,* 2017); and postmenopausal hypertension (July *et al.,* 2017); and association among adipokines and hypertension (Xia *et al.,* 2015). Adipokines are involved in the pathogenesis of a variety of disorders including obesity, arterial hypertension, atherosclerosis, diabetes mellitus, heart failure and hyperlipidemia (Bełtowski, 2006a, b) and some of these substances e.g. leptins are considered both dependent predictors (for obesity and other factors) (Momose *et al.,* 1999; Itoh *et al.,* 2002; Haque *et al.,* 2006; Nakamura *et al.,* 2009; Atwa *et al.,* 2014; Vaněčková *et al.,* 2014; Kerimkulova *et al.,* 2014; Bell and Rahmouni, 2016) and independent predictors (for endothelial and immune factors) (Kazumi *et al.,* 1999; Schutte *et al.,* 2005; Dubey and Hesong, 2006; Thomopoulos *et al.,* 2009; Bełtowski, 2006a,b ; Kartal *et al.,* 2008; Olszanecka *et al.,* 2010; Bełtowski, 2012; Karbowska and Kochan, 2012; Allison *et al.,* 2013; Rahma *et al.,* 2013) for endothelial function/ dysfunction in normotensives.

Controversial results for the association of adipokines have been documented. e.g. acute administration of leptin showing no effect on blood pressure (Bełtowski, 2006a). Most of the information about leptin-sympathetic and leptin-resistance actions have been predicted on the bases of in vitro and animal studies, and it is essential to have data from humans studies (Correia and Haynes, 2004). However, there are reports showing contradictory results for the regulation of blood pressure and vice versa. e.g. among the subjects with higher blood pressure, neither the

association of leptin with systolic blood pressure nor with diastolic blood pressure was found statistically significant (Wada *et al.,* 2006). Leptin serves as a mediator for obesity induced hypertension (Bell and Rahmouni, 2016).

Adiponectin has been shown associated in: a) subjects with blood pressure changes (Kazumi *et al.,* 2002; Iwashima *et al.,* 2004; Jung *et al.,* 2004; Chow *et al.,* 2007; Li *et al.,* 2007; Nishida *et al.,* 2007; Díez and Iglesias, 2010; Xia *et al.,* 2015); b) obese subjects with blood pressure changes (Kazumi *et al.,* 2002; Nishida *et al.,* 2007; Celoria *et al.,* 2010; Ding *et al.,* 2012; DeMarco *et al.,* 2014; Di Chiara *et al.,* 2014; de Faria *et al.,* 2014; c) subjects with blood pressure changes due to decreased HDL cholesterol (Lee *et al.,* 2007); d) subjects with hypertension partly independent of obesity (Brambilla *et al.,* 2013); e) subjects with normal blood pressure independently of adiposity (Sung *et al.,* 2008); f) in subjects with hypertension with endothelial dysfunction (Rojas *et al.,* 2014); g) subjects with pre-hypertension with obesity of multiethnic origin (Celoria *et al.,* 2010).

It has been shown that adiponectin is not associated with blood pressure changes in normotensive and untreated hypertensives even after adjusting for the other risk factors (Ivković *et al.,* 2014), whereas another report reveals that it is not involved in overweight hypertensives (Seven *et al.,* 2014). Furthermore, high adiponectin levels failed to protect the subjects with hypertension (Onat *et al.,* 2013).

Other adipokines involved in the regulation of blood pressure are: plasma apelin (Kalea and Batlle, 2010; Cudnoch *et al.,* 2011; Cao *et al.,* 2014; Papadopoulos *et al.,* 2014), and plasma resistin (Furuhashi *et al.,* 2003; Papadopoulos *et al.,* 2009; Iacobellis *et al.,* 2010).

In view of the mentioned reports, different other reports providing positive or negative role of adipokines in the progression of blood pressure leading to high-normal blood pressure, prehypertension and hypertension, and some of the controversial results, we planned to carry out a comprehensive review study for uncovering new information and providing further information regarding the role of some of the adipokines (mainly adiponectin, leptin, apelin, and resistin) and related systemic changes in human subjects.

Adipocytokines

Adipokines or adipocytokines are the proteins secreted from adipose tissue. The important adipokines are: leptin, adiponectin, resistin, apelin, interleukin-6, chemerin, visfatin, tumor necrosis factor-alpha and a variety of others. We will discuss here only the role of leptin, adiponectin, apelin and resistin in the regulation of blood pressure.

Adipose tissue secreted hormones or now termed as adipokines, the discovery of which followed the discovery of leptin twenty years ago are significant for future investigation approaches for precise understanding of the action for adipokines (Blüher and Mantzoros, 2015). Adipose tissue does not serve only as a storage depot for energy, but also actively involved as an endocrine tissue (Ding *et al.,* 2012). Relay information about energy stores to the peripheral tissues in body is the specific activity of adipokines, hormones and cytokines secreted from adipocytes (Ding *et al.,* 2012). Adipocytokines are the active biological substances secreted from adipose tissue that act in an autocrine, endocrine and paracrine manner (Cinar and Gurlek, 2013). The major role of adipokines is in appetite control, thermogenesis, thyroid functions (associated with changes in body weight, energy expenditure and thermogenesis; abnormal level of leptin, adiponectin, visfatin, resistin, vaspin, and other adipocytokines in hypo- and hyperthyroidism), reproductive functions, generalized inflammation, obesity related vascular disorders e.g. insulin resistance, atherosclerosis, hypertension, diabetes, dyslipidemia, impaired glucose tolerance etc. (Cinar and Gurlek, 2013).

Leptin is a 16-kDa protein and an adipocytokine produced mainly in white adipose tissues though also produced in the brown adipose tissues and in a variety of body organs (Margetic *et al.,* 2002). It is 167-amino acid protein present in our body in free form and bound with proteins (Sinha *et al.,* 1996). It is involved in the pathogenesis of hypertension and cardiovascular diseases, regulates food intake and energy expenditure (Bełtowski, 2006a) and fat stores and performs several other functions (Maffei *et al.,* 1995). Plasma leptin level is proportional to the amount of adipose tissue and it is increased markedly in obese people (Bełtowski, 2006a).

Adiponectin, a 244-amino-acid polypeptide was discovered first in 1995 and characterized later in various cells (Scherer *et al.,* 1995; Matsuzawa *et al.,* 2004; Lara-Castro *et al.,* 2007). It is secreted from adipose tissues and also from placenta in pregnancy (Chen *et al.,* 2006) into blood and modulates glucose regulation and fatty acid breakdown (Díez and Iglesias, 2003) and is involved in a number of other metabolic processes. Adiponectin, a cardioprotective adipokine is a collagen-like protein expressed in adipose tissue (Díez and Iglesias, 2010).

Apelin, an endogenous ligand for the G-protein-coupled APJ receptor (Szokodi *et al.,* 2002; Kleinz and Davenport, 2005) was identified and discovered in 1998 by Professor M. Fujino's team (Tatemoto *et al.,* 1998). It has been found that vascular expression of apelin receptor (Devic *et al.,* 1999; Saint-Geniez *et al.,* 2002) is involved in the regulation of blood pressure (Lee *et al..,* 2000). Hypotensive effect of apelin on the surfaces of endotheliel

cells (Devic *et al.,* 1999; Saint-Geniez *et al.,* 2002) causes release of NO (Tatemoto *et al.,* 2001) that helps lowering blood pressure.

Resistin also called as adipose tissue-specific secretory factor (ADSF) was discovered in 2001 by Dr Mitchell A. Lazar and group from the University of Pennsylvania, School of Medicine (Steppan *et al.,* 2001). It is specifically involved in the inflammatory response (Malyszko *et al.*, 2006; Nagaev *et al.,* 2006; Kusminski *et al.*, 2007).

Adipocytokines, blood pressure variations and hypertension

Association of adipocytokines with hypertension (Xia *et al.,* 2015; Serafi *et al.,* 2016), cardioprotective effects of adipocytokines (Dutheil *et al.,* 2017; Lau *et al.,* 2017), and role of adipocytokines in primary arterial hypertension (Jedzura *et al.,* 2017) and postmenopausal hypertension (July *et al.,* 2017) are the important aspects related to hypertension and adipokines.

Obesity-associated hypertension has been explained by linking the microvascular and perivascular adipose tissue inflammation with the synthesis of adipokines e.g. leptin, adiponectin, resistin, visfatin, and other cytokines e.g. IL-6, TNF-α, IL-1, MCP-1 etc. (Kang, 2013; Bell and Rahmouni, 2016). Beside other mechanisms, abnormal level of leptin and certain other cytokines effecting at the vascular endothelial level are related to obesity-related hypertension (Vaněčková *et al.,* 2014). Hypertension and other cardiac dysfunction have been related to increased plasma leptin levels, and leptin is considered as independent risk factor for the coronary heart disease, though it was suggested for conducting additional studies incorporating caloric restriction and weight loss for reducing the plasma leptin levels (Karbowska and Kochan, 2012).

Leptin serves as a mediator for obesity induced hypertension (Bell and Rahmouni, 2016). Higher leptin value is an independent predictor of PAD (peripheral artery disease) in hypertensive patients (Huang *et al.,* 2017). Hyperleptinemia is involved in endothelial dysfunction especially in hypertensive obese patients (Freitas Lima *et al.,* 2015). Leptin levels were found to be higher in patients with uncontrolled hypertension (HTN) as compared to those with controlled HTN (Sabbatini *et al.,* 2014), and hyperleptinemia revealed as a predictor for arterial stiffness in hypertension patients (Tsai *et al.,* 2016) and noted as a critical factor in insulin resistance (Freitas Lima *et al.,* 2015).

Association of blood pressure, BMI and plasma leptin levels in young normal weight male subjects has been investigated (Serafi *et al.,* 2016). Association of leptin, hypertension and obesity studied in a Kyrgyz group by weight, height, waist/ hip circumference, BMI, blood pressure, fasting plasma glucose and serum leptin measurements showed elevated leptin level associated with the higher risk of hypertension and correlated with BMI and waist circumference, systolic blood pressure and diastolic blood pressure (Kerimkulova *et al.,* 2014). Leptin levels obtained were similar in obese African and Caucasian women, but leptin is associated favorably to vascular function in obese Caucasians, but not in obese Africans (Schutte *et al.,* 2005). Increased serum leptin was found to be associated with tachycardia and increases in both systolic and diastolic blood pressure in obesity through complex mechanisms (Haque *et al.,* 2006).

How to improve the health and especially the cardiovascular health in the next generation has been explained by suggesting unraveling the role of adiopocytokines in heart disease, endothelial dysfunction, hypertension and atherosclerosis (Van de Voorde *et al.,* 2013). It has been suggested that the excessive adipocyte hypertrophy due to obesity may cause hypoxia in adipose tissue and that might cause adiposopathy, and hence, the healthy adipose tissue producing more release of healthy adipokines is converted into sick adipose tissue producing less release of healthy adipokines e.g. adiponectin and omentin and more release of unhealthy adipokines (Van de Voorde *et al.,* 2013).

Abnormal variations in the adipokines leptin, resistin, and adiponectin can lead to the clinical characteristics frequently recognized in resistant hypertension (de Faria *et al.,* 2014). Hence, any approach to regulate adipokines might be fruitful for the management of resistant hypertension (de Faria *et al.,* 2014). Leptin is considered important in regulating the endothelial functions (e.g. hypertension and atherosclerosis) in normal and abnormal conditions (Bełtowski, 2012).

Physiological and pathological conditions have been interpreted involving leptin causing the endothelium dependent vasorelaxation and impairment in vasodilatory effect respectively and a major cause leading to arterial hypertension (Bełtowski, 2012). It has been noted that atherosclerosis constitutes a variety of factors including mainly the inflammation and endothelial dysfunction causing hardening and thickening of the vessels, and may lead to loss of elasticity and decrease in the lumen of the vessels (Dubey and Hesong, 2006).

It has been reviewed (Dubey and Hesong, 2006) that atherogenic mechanism of leptin and the beneficial role of statins are related via the involvement of leptin in increasing the oxidative stress and blood pressure. Free leptin has similar leptin related vascular impairment as it was found almost equally increased in masked as well as sustained hypertension in nonobese subjects (Thomopoulos *et al.,* 2009). Plasma leptin levels are important in the regulation

of blood pressure in women, differential distribution/ activity of leptin in women and men and gender differences in hypertension (Ma *et al.,* 2009).

Leptin is important in understanding the regulation of blood pressure (Serafi *et al.,* 2016) and pathophysiology of arterial hypertension irrespective of obesity and body adiposity both in normotensives and in hypertensives (Bełtowski, 2006a). Hyperleptinemia independent of body fat or body mass index may be a regulator of arterial pressure (Kazumi *et al.,* 1999).

It was further viewed that acute administration of leptin showing no effect on blood pressure, might be due to its concomitant stimulation to the sympathetic nervous system and involvement of natriuresis and nitric oxide (NO)-dependent vasorelaxation, and the elevation of blood pressure by chronic hyperleptinemia is probably due to impairment of acute depressor effects and appearance of sympathetic nervous system-independent pressor effects additionally, e.g. oxidative stress, more production of endothelin, NO deficiency, and increased renal Na reabsorption (Bełtowski, 2006a, b).

Most of the information about leptin-sympathetic and leptin-resistance actions have been predicted on the bases of *in vitro* and animal studies, it is essential to have data from humans studies (Correia and Haynes, 2004). Sympathetic actions of leptin explain a relevant mechanism for the regulation of blood pressure and leptin resistance. However, disturbance in the intracellular signaling pathways and resistance of specific leptin-responsive neural networks provide a better approach to understand selective leptin resistance (Correia and Haynes, 2004).

The topics of the regulation of blood pressure, sexual maturation and angiogenesis relate to possible involvement of leptin as it is predicted from experimental studies that leptin represents hematopoietic factor via the long isoform of leptin receptor belonging to cytokine receptors group, though not investigated in clinical studies. This necessitates to explore the role of leptin in various phases of hematological diseases and during the treatment of these diseases (Haluzík *et al.,* 2000). It has been investigated that serum leptin levels increase in patients with hypertensive intracerebral haemorrhage (Zhao *et al.,* 2012).

In view of the contribution of leptin in sympathetic control of blood pressure, it was tried to confirm whether the loss of leptin is involved in hypotension in patients with multiple system atrophy frequently exhibiting orthostatic hypotension (Ozawa *et al.,* 2014). However, results did not prove that. The circulating leptin level preserved and hypotension was found to occur independent of the involvement of leptin in patients with multiple system atrophy (Ozawa *et al.*, 2014).

A study to assess the relationship between adipocytokine levels and blood pressure, serum lipid and glucose in middle-aged perimenopausal women having essential hypertension, showed the strongest predictors as waist circumference and serum leptin levels, and apparently the association of adiponectin and resistin concentration with blood pressure values could not be obtained, that also indicates that hypertensive postmenopausal females showing increased leptin concentration have important role in the pathogenesis of hypertension, independent of BMI (Olszanecka *et al.,* 2010).

Due to contradictory results on the association of leptin with dyslipidemia, a study comprising serum leptin, body height, weight, BMI waist circumference, hip circumference, blood pressure, plasma glucose (fasting), lipid profile (total cholesterol , triglycerides, high-density lipoprotein, cholesterol, low-density lipoprotein cholesterol), showed leptin positively correlating with BMI, waist circumference and triglycerides in both sexes of Kyrgyz and with total cholesterol in Kyrgyz males (Mirrakhimov *et al.,* 2014).

Relationship between fasting serum leptin and peripheral arterial stiffness in kidney transplant patients showed hypertension, age, triglyceride levels, systolic blood pressure, waist circumference, and leptin level higher, whereas serum high-density lipoprotein cholesterol level lower in the high arterial stiffness group compared to low arterial stiffness group and it was found that leptin and high-density lipoprotein cholesterol level were independent predictors for peripheral arterial stiffness (Lee *et al.,* 2014). Leptin might be an independent mediator for obesity-related elevations in blood pressure (Nakamura *et al.,* 2009).

While investigating the relationship between the elevation in blood pressure and serum leptin due to the influence of noise in work place, it was found that systolic blood pressure and diastolic blood pressure had a significant correlation with leptin levels compared to the control possibly under the influence of sympathetic nervous system and involvement of leptin in diverse cardiovascular actions (Rahma *et al.,* 2013).

A study for determining serum leptin, adiponectin, and resistin, and correlations of these adipokines with insulin resistance and other risk factors for cardiovascular disease in patients with Acanthosis nigricans, showed significant variation between Acanthosis nigricans patients and obese controls in serum leptin, adiponectin, and resistin. Significant positive correlations between serum leptin and glucose, insulin, BMI, low-density lipoprotein and cholesterol, and significant negative correlations between adiponectin and insulin, cholesterol, BMI, and leptin in patients with Acanthosis nigricans were obtained (Atwa *et al.,* 2014).

Serum levels of angiotensin II in lean females and angiotensin II and leptin as well in obese subjects were noticed as strong predictor of blood pressure (Al-Hazimi and Syiamic, 2004). Leptin may play a prominent role in the pathophysiology of hypertensives with obesity and after weight loss (Itoh *et al.,* 2002). Serum leptin has significant gender based differences and it correlates positively with body fat. However, it is still not verified whether leptin levels are independently related to eating behavior, physical activity, serum lipids and blood pressure (Momose *et al.,* 1999).

Examining the associations among blood pressure and leptin, resistin, tumor necrosis factor-α (TNFα), and total adiponectin in a multiethnic study of atherosclerosis, higher level of leptin was found significantly associated with higher systolic, diastolic, mean arterial and pulse pressures as well as higher odds for hypertension (Allison *et al.,* 2013). The results indicated that: leptin and hypertension strongly associated in men, though not varying by BMI, race/ethnic group, or smoking status; adiponectin, resistin and TNFα not associated independently with blood pressure / hypertension; higher serum leptin, but not resistin, adiponectin, or TNFα, associated with higher blood pressure / higher odds of hypertension, independent of risk factors, other adipokines and anthropometric measures (Allison *et al.,* 2013).

Obstructive sleep apnea hypopnea syndrome might affect blood pressure independently, particularly DBP, after waking up, and serum leptin may be the independent correlate of hypertension in such conditions (Huang *et al.,* 2010).

Elevated levels of serum leptin are significantly related with left ventricular hypertrophy independently of level of blood pressure and body mass index (Kartal *et al.,* 2008). Circulating leptin is related to body fatness, but the hypertensive influence of leptin can be modified by physical exercise and fitness (Sabatier *et al.,* 2008). hyperleptinemia was found a significant risk factor for high blood pressure in elderly individuals mainly the male subjects (Mendoza-Núñez *et al.,* 2006). Among the subjects with higher blood pressure, however, neither the association of leptin with systolic blood pressure nor with diastolic blood pressure was found statistically significant (Wada *et al.,* 2006).

Adiponectin is a cardioprotective adipokine, and is produced in inverse proportion to fat mass in contrast to the secretion of leptin and other adipokines that are produced in direct proportion to fat mass, or as a proinflammatory or have adverse actions on cardiovascular system i.e. circulating adiponectin highest in lean individuals as inversely correlating with fat mass (Ding *et al.,* 2012). This shows that the low levels of serum adiponectin might be considered as a risk factor in a variety of cardiovascular diseases including coronary artery disease and hypertension (Ding *et al.,* 2012).

Adiponectin is a collagen-like protein expressed in adipose tissue (Díez and Iglesias, 2010). Adiponectin is considered as a cardioprotective factor in the health state, as the low serum adiponectin showed association with insulin resistance, arterial hypertension and atherogenic hyperlipidemia whereas high serum adiponectin expressed a reduced risk of myocardial infarction (Díez and Iglesias, 2010), and hypertension (Peri-Okonny *et al.,* 2017; Yin *et al.,* 2017).

Functions of adiponectin had been unclear, though it has been clinically shown that serum adiponectin is inversely associated with body weight, particularly abdominal the visceral fat accumulation (Nishida *et al.,* 2007). Blood pressure, insulin resistance, low-density lipoprotein (LDL) cholesterol, triglyceride levels and other cardiovascular risk factors are inversely associated with adiponectin levels, and HDL cholesterol positively associated (Nishida *et al.,* 2007). Adiponectin serving as antiatherogenic and anti-inflammatory agent and its other cardiovascular and metabolic attributes reveal that adiponectin may become a promising therapeutic target for preventing cardiovascular diseases (Nishida *et al.,* 2007).

Some of the recent studies reveal adiponectin in obese children in relation to blood pressure (Yin *et al.,* 2017), protection of incident hypertension by adiponectin independent of body fat distribution (Peri-Okonny *et al.,* 2017), association of adiponectin with arteriolar vessel caliber in hypertensive subjects (Beltrami-Moreira *et al.,* 2015) and hypertension associated with adiponectin polymorphism (Wu *et al.,* 2017).

Mean blood pressure negatively correlated with the serum level of adiponectin (Li *et al.,* 2007; (Peri-Okonny *et al.,* 2017; Yin *et al.,* 2017). The normotensives with low levels of adiponectin had an increased risk of becoming hypertensives that suggests the pathogenetic involvement of hypoadiponectinaemia in the development of hypertension (Chow *et al.,* 2007). High normal range blood pressure in young men showed lower serum adiponectin and faster heart rate even after adjusting for BMI (Kazumi *et al.,* 2002). While investigating the role of adiponectin in normotensives leading to hypertension, low level of adiponectin was found associated with the increased risk of new onset hypertension (Jung *et al.,* 2004). Hypoadiponectinemia is a marker for predisposition to men with hypertension (Iwashima *et al.,* 2004).

Hypoadiponectinemia was found associated with pre-hypertension in obese subjects of multiethnic origin (Celoria *et al.,* 2010). Adiponectin including leptin, resistin, IL-6, TNF and others, which cause exacerbation in

obesity-associated cardiovascular disease are found involved in obesity-related hypertension (DeMarco *et al.,* 2014). It was investigated that plasma levels of adiponectin were significantly lower in hypertensives associated with visceral obesity than in lean normotensives and lean hypertensives (Di Chiara *et al.,* 2014). Aldosterone excess and inflammatory adipocytokines including mainly leptin, resistin, and adiponectin in association with the hyperactivity of sympathetic and renin-angiotensin-aldosterone systems, and vascular damage have a significant role in causing obesity-related hypertension (de Faria *et al.,* 2014).

Serum adiponectin level in middle-aged Korean women was found decreased with low HDL-cholesterol and may be considered as an independent risk factor for hypertension (Lee *et al.,* 2007). Patients with metabolic syndrome showed hypo-adiponectinaemia, and hyperresistinaemia. However, the elevated resistin levels might be involved in hypertension (Musialik, 2012). While studying the different clinical blood pressure phenotypes, hypertensive and masked hypertensive compared to normotensive phenotype showed independent association with resistin and adiponectin concentrations (Thomopoulos *et al.,* 2011).

In an aim to reveal association between adiponectin, lipid profile, blood pressure and BMI, adiponectin, in type 2 diabetics compared to control subjects showed significant variations in mean adiponectin for gender and different ethnic and age groups (Nayak *et al.,* 2012).

Adiponectin is considered quite involved in hypertension (Peri-Okonny *et al.,* 2017; Yin *et al.,* 2017) through endothelial dysfunction (Rojas *et al.,* 2014). An inverse relationship between serum adiponectin and hypertension in 5-18 years children partly independent of obesity has been documented (Brambilla *et al.,* 2013). A negative correlation of adiponectin levels with waist circumference and a negative correlation of adiponectin as well as leptin with waist-to-hip ratio were observed in hypertensives with obesity (Stępień *et al.,* 2012). Adiponectin, but not leptin was found associated with blood pressure in nondiabetic normotensives independently of adiposity (Sung *et al.,* 2008). Leptin, but not adiponectin and other factors might be involved in overweight hypertensives (Seven *et al.,* 2014).

It was noted that adiponectin, in normotensives and untreated hypertensives with normal kidney function, is not associated with blood pressure even after adjusting for the other risk factors (Ivković *et al.,* 2014). To investigate the involvement of serum adiponectin in protecting against hypertension, it was revealed that high adiponectin levels failed to protect against the risk of hypertension (Onat *et al.,* 2013).

The peptide apelin is an endogenous ligand for the receptor APJ (Kalea and Batlle, 2010). Apelin and APJ have been found as localized in cardiomyocytes and vascular cells and this system may be an important for the regulation of vascular tone, blood pressure and cardiovascular function (Kalea and Batlle, 2010).

Apelin has positive inotropic effect on cardiomyocytes, vasodilation while acting directly on smooth muscle cells, and vasodilatory action in the endothelium where it releases nitric oxide (Cudnoch *et al.,* 2011). Apelin interacts with other compounds e.g. angiotensin II, vasopressin, and sympathetic nervous system for the regulation of blood pressure. It is especially found involved in hypertension, ischemic heart disease, and initial stages of heart failure (Cudnoch *et al.,* 2011). However, further experimental and clinical studies will present the positive and negative role of apelin in the metabolic and cardiovascular diseases (Cudnoch *et al.,* 2011).

Apelin agonists for orphan receptor APJ has been discovered in several isoforms in the central nervous system and in different peripheral tissues (Cudnoch *et al.,* 2011). In the cardiovascular system apelin peptide is found in heart and endothelium and smooth muscles cells of vascular wall (Cudnoch *et al.,* 2011).

The apelin receptor APJ has a high sequence similarity to angiotensin receptor AT1 and is originally a class A, rhodopsin-like G protein-coupled receptor (GPCR). APJ widely expresses in humans tissues, including the central nervous system, adipocytes, cardiovascular and other systems (Cao *et al.,* 2014).

APJ is associated with the occurrence of metabolic and cardiovascular diseases mainly atherosclerosis, heart failure, coronary heart disease, pulmonary arterial hypertension, myocardial hypertrophy and atrial fibrillation, especially hypertension. The mode of the action of Apelin/ APJ is to produce vasodilation and reduce blood pressure levels. Despite finding APJ closely related with many diseases, there are no drugs that can activate or inhibit APJ directly. Hence, there is a need of developing compounds based on APJ for treatment of diverse diseases (Cao *et al.,* 2014).

Some of the major actions of apelin include: endothelial depending nitric oxide mediated-vasorelaxation, involved in reducing arterial blood pressure, causing long lasting and positive ionotropic action even in injured myocardium but not accompanying myocardial hypertrophy, action of inhibiting the production of vasopressin and intake of water and up-regulated in obesity (Bełtowski, 2006b). Plasma levels of apelin were found decreased in non diabetic, non obese and normotensive patients showing increased LDL cholesterol (Tasci *et al.,* 2007). The healthy and young offspring of healthy parents showed significantly lower plasma level of apelin compared to the healthy and young offspring of hypertensive patients (Papadopoulos *et al.,* 2014). In connection with some of the findings that apelin causes endothelium dependent vasorelaxation, decreases the arterial blood pressure, and acts as vascular

regulator, it has further been found that apelin level is decreased in patients with masked hypertension (Papadopoulos *et al.,* 2013).

Decrease in plasma apelin levels in patients having essential hypertension suggests its independent association with the impairment of left ventricular systolic and diastolic function (Przewlocka-Kosmala *et al.,* 2011). Apelin levels were found significantly lower in the patients with essential hypertension, and related to the systolic blood pressures (Sonmez *et al.,* 2010). The deoxycorticosterone acetate-salt-induced hypertensive rats showed that apelin decreases blood pressure which suggests the possibility of using apelin for the treatment of hypertension (Akcılar *et al.,* 2013). The influence of exercise training on the apelin/APJ system in hypertensive rats showed expression of apelin/AJP in cardiovascular tissues (Zhang *et al.,* 2006).

Prehypertensive healthy subjects have significantly lower adiponectin and significantly higher resistin plasma levels compared with normotensive healthy subjects (Papadopoulos *et al.,* 2009). Higher resistin and lower adiponectin levels in masked hypertensives compared with normotensive individuals was suggested that revealed the prognostic importance for future cardiovascular discomforts in masked hypertensives (Papadopoulos *et al.,* 2009).

The hypertensives revealed significant positive correlation for leptin vs body mass index and leptin vs body adiposity index whereas the normotensives showed leptin positively correlating with body adiposity index and negatively correlating with waist-to-hip ratio, adiponectin negatively correlating with waist-to-hip ratio , and resistin negatively correlating with waist-to-hip ratio. In general, the obese hypertensives showed visceral obesity and leptin associated with hypertension (Stepien *et al.,* 2014). Plasma resistin was significantly higher in primary aldosteronism subjects when compared with essential hypertension with/ without metabolic syndrome (Iacobellis *et al.,* 2010). Circulating resistin levels at least in essential hypertensive patients could not be found related to BMI, blood pressure, insulin resistance and lipid variables (Furuhashi *et al.,* 2003).

Conclusions

Various phenotypes of blood pressure manifestation (normotension, masked hypertension, high-normal blood pressure, prehypertension, hypertension, resistant hypertension etc) have provided confusing and misleading results in certain occasions. Studies present positive as well as negative effect of adipokines in initiating the dysfunctions leading/ progressing to high-normal blood pressure, prehypertension and hypertension. It is alarming that clinical and basic/ experimental research could not lead us to the intricate etiology/ pathophysiology of hypertension though it is considered as a main risk factor for cardiovascular disease.

Similarly, results obtained for plasma adipokines by different researchers are not similar e.g. leptins are considered both dependent predictors (for obesity and other factors) and independent predictors (for endothelial and immune factors) of endothelial function/ dysfunction in normotensives. Whereas, controversial results for the association of adipokines has been documented. e.g. acute administration of leptin showing no effect on blood pressure.

Most of the information about leptin-sympathetic and leptin-resistance actions has been predicted on the basis of in vitro and animal studies, and it is essential to have data from human studies. There are reports showing contradictory results for the role of adipokines in the regulation of blood pressure and vice versa. e.g. among the subjects with higher blood pressure, neither the association of leptin with systolic blood pressure nor with diastolic blood pressure was found statistically significant.

Decreased levels of plasma adiponectin associated with blood pressure changes with obesity or without obesity; due to some other cause as decreased HDL-cholesterol; or due to endothelial dysfunction etc show obvious controversial aspects. Furthermore, no association of adiponectin with blood pressure changes in normotensive and untreated hypertensives even after adjusting for the other risk factors; and not involved in overweight hypertensives has been documented. Whereas it was also revealed that high adiponectin levels could not protect the subjects with hypertension.

Decreased plasma levels of apelin are though considered as involved in stabilizing the normal blood plod pressure in normotensives as well as masked hypertensives; and increased levels in hypertensives and healthy and young offspring of hypertensive patients. There are reports, however, that reveal decreased apelin levels obtained in the patients with essential hypertension, and related to the systolic blood pressures. Mode of action of apelin for decreasing blood pressure seems the action of apelin receptors to produce vasodilation and reduction in blood pressure and causing endothelium dependent vasorelaxation. However, there are no drugs that can activate or inhibit apelin receptors (APJ) directly and hence, there is a need of developing compounds based on APJ for treatment of diverse diseases. This has been supported by the findings that hypertensive rats showed decrease in blood pressure by using epelin, and hence, a possibility of using apelin for the treatment of hypertension.

A little information is available about the actions of resistin associated with the blood pressure changes. Higher plasma resistin levels were found in prehypertensives compared with healthy normotensive subjects; and subjects

with primary aldosteronism when compared with essential hypertension with/ without metabolic syndrome. However, controversy exists here as well. Resistin has also been found unrelated to blood pressure, BMI, and lipid variables in essential hypertensive patients.

Information provided in the current review indicates that available information about the role of adiponectins in blood pressure regulation is not sufficient and hence, further studies are essentially required to be conducted in various perspectives to understand the clear role and regulation of adipocytokines mainly in normal healthy people, people having blood pressure variations, and people with hypertension.

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(*Accepted for publication November 2017*)