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Ghrelin, obesity and atherosclerosis

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ABSTRACT

Cardiovascular disease (CVD) is the largest single cause of mortality in human population and its major underlying pathology is atherosclerosis. Atherosclerosis is a chronic inflammatory disease that predisposes to coronary artery disease (CAD), stroke and peripheral arterial disease, responsible for most of the cardiovascular morbidity and mortality. It is an inflammatory process, triggered by the presence of lipids in the vascular wall, and encompasses a complex interaction among inflammatory cells, vascular elements, and lipoproteins through expression of several adhesion molecules and cytokines. Atherosclerosis is initiated by an accumulation of lipids, necrotic cells and fibrous elements in the neointima of medium and large arteries. Obesity *per se* is a strong risk factor for CVD. The pathophysiological mechanisms of the association between obesity and atherosclerosis are not fully understood. Altered levels of obesity related peptides such as ghrelin may play an important role in this pathophysiology. Recent evidence indicates that ghrelin feature a variety of cardiovascular activities, including increase of

myocardial contractility, vasodilatation, and protection from myocardial infarction. Recent literature data demonstrate that ghrelin can influence important key events in atherogenesis and thus they may play a role in atherosclerosis. In this review we present the latest data from recent performed animal and clinical studies which have focus on a novel approach to ghrelin as potential therapeutic agents in the treatment of complex disease such as atherosclerosis. Future investigations should now focus on the mechanisms of ghrelin actions which might present new approaches involved in the antiatherosclerotic effects revealed in this review. Thus, ghrelin may become a new therapeutic target for the treatment of some cardiovascular diseases. Further studies are necessary to investigate the potential mechanisms for the effects of ghrelin on cardiovascular system (CVS).

Key words: Ghrelin, obesity, atherosclerosis, cardiovascular disease

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1. Introduction

Cardiovascular disease (CVD), including coronary artery disease (CAD), stroke, and ischemia, are the leading single cause of morbidity and mortality in western world [1, 2]. The major underlying pathological feature of these multifactorial diseases is atherosclerosis [2].

Atherosclerosis is a chronic inflammatory disease, described as occlusions of lipids andinflammatory cells within the intimal layer of vascular wall which results in endothelial cell injury and tissue dysfunction, leading to thickening and hardeningof the vessel wall [3]. Atherosclerotic plaque formation (hard structures in the walls) in small and large arteries, encompasses a complex interaction among vascular elements, inflammatory cells, and lipoproteins through expression of several adhesion molecules and cytokines [4]. Over time, these plaques can block the arteries and cause symptoms and problems throughout the body. It has become obvious that atherosclerosis is a multifactorial disease that involves not just genetic predisposition, but also environmental factors. Several already established factors contribute to the development of atherosclerosis [3]. The major risk factors for atherosclerosis are well-known and include high blood pressure, abnormal blood lipid profile (high total and low density lipoprotein (LDL) cholesterol and triglyceride concentrations and low high density lipoprotein (HDL) cholesterol concentration), smoking, physical inactivity, unhealthy diet (low intake of fruits and vegetables) and diabetes mellitus. In addition, the non-modifiable risk factors include advancing age, gender and family history of premature CAD. Importantly, inflammation is now believed to be a novel risk factor [5].

Beside well known risk factors for the development of atherosclerosis, obesity has an important role to, but also, obesity, especially abdominal obesity, *per se* is a strong undependent

risk factor for CVD and many studies have shown the link betwen increased mortality and morbidity of CVD and obesity [6-11]. Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health [12]. Obesity is a chronic multifactorial and complex disease, resulting from a long-term positive energy balance in wich bouth genetic and enviromental factors are involved [13-15]. It has been recently suggested that some forms of obesity are associated with chronic low-grade inflammation [13, 16]. The pathophysiological mechanisms of the association between obesity and atherosclerosis are not fully understood.

It is possible that inflammation induced by obesity accelerates the atherosclerosis development [13]. Adipose tissue is recognized as an important player in obesity mediated CVD, becouse adipocytes produce large number of hormons, peptides and other molecules that effects cardiovascular system (CVS) function not only in endocrine manner, but also by autocrine and paracrine mechanisms [13, 17]. All this can lead to cytokine-mediated inflammatory changes in the liver, systemic infflamation and atherosclerosis [13]. Altered levels of obesity related peptides such as ghrelin, may play an important role in this pathophysiology [18].

Ghrelin is a gastric peptide hormone found in 1999. which has been shown to be associated with obesity. Ghrelin is consisting of 28 amino acids, among which the third amino acid Serin-3 (Ser^3) is n-octanoylated, modified by a fatty acid and this modification is essential for ghrelin's activity. Ghrelin is a growth hormone (GH) secretagogue which stimulates the release of GH from the pituitary and acts through the GHS-receptor (GHS-R), type 1a (GHS-R1a) which is a G protein coupled receptor. The tissue distribution of ghrelin and GHS-R1a is widespread, but it is mainly produced in the stomach and GHS-R1a is mainly expressed in hypothalamus and in the pituitary, but GHS-R1a is also present in cardiomyocytes [19-21].

Recent evidence indicates that ghrelin, features a variety of cardiovascular activities, including increase of myocardial contractility, vasodilatation, and protection from myocardial infarction. It has been shown that ghrelin may have an important role in cardiovascular function, including regulation of atherosclerosis [22-25]. In addition, it has been shown that ghrelin stimulates appetite by acting on the hypothalamic arcuate nucleus, a region known to control food intake. Plasma ghrelin levels are decreased in obesity and increased under negative energy balance [26]. Ghrelin beside regulation of appetite affects secretion of gastric acid, gastric movement [20, 21]. Interestingly, ghrelin has been claimed to have anti-inflammatory actions that may have an important role in the development of atherosclerosis [27].

Favorable effects of ghrelin on the CVS have been shown both in humans and on animal models. Taking into consideration that ghrelin stimulates GH release, which earlier proved to have cardioprotective effects [28-30], ghrelin could possibly show favorable effects on CVS mediated through GH, but it could also show effects independent of GH effects [31-33]. It has been shown that ghrelin may improve cardiac function partly through GH dependent mechanisms but also, some evidence suggests that ghrelin's cardioprotective activity is independent from GH secretion[31-33]. It was earlier shown that GH has a favorable effect on the positive outcome in patients with heart disease [30].

Present chapter reviews, in a concise form, the latest data from recent performed animal and clinical studies which have focus on a novel approach to ghrelin as potential therapeutic agents in the treatment of complex disease such as atherosclerosis.

2. Ghrelin and obesity

Obesity and obesity related diseases are a major public health problem all around the world [34]. The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended [35, 36]. According to World Health Organization (WHO), overweight and obesity are the fifth leading cause for deaths on global level and considering its spreading it became a serious health problem and it is one of the major risk factors for the development of CVD like hypertension and atherosclerosis, and also diabetes [35].

The presence of obesity has been long associated with the presence of endothelial and vascular dysfunction, which provides partial explanation of how may obesity lead to CVD [34, 37-39]. Obesity has many negative effects on the hemodynamic and also on the structure and function of the CVS [40]. In addition, in many epidemiological studies on obesity, it has been shown that obesity predisposes to CVD [36]. Although the associations of obesity and vascular dysfunction and vascular disorders have been unquestionably proven in large clinical trials, the exact mechanisms by which obesity leads to them, and therefore prospects for therapeutic interventions remain poorly explained [34].

Recent studies have shown that adipose tissue is not a simple energy storage organ, but exerts important endocrine and immune functions [34]. It is possible that alterations of immune function can link obesity to vascular disorders and risk factors for atherosclerosis [34, 41]. Indeed, recent data show that adipocytes as well as other cells present within fat tissues, are capable of releasing numerous novel and highly active molecules which acts as vasoactive factors leading to cardiovascular morbidity in obese individuals [34]. These adipocyte derived products exert significant effects on the immune system, thus modifying inflammation. These factors are termed “adipocytokines” in relation to fat tissue being their source [34, 42].

Adipocytokines include several molecules released abundantly by adipocytes like leptin, resistin, adiponectin or visfatin, as well as some more classical cytokines released possibly by inflammatory cells infiltrating fat, like tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), monocyte chemotactic protein-1 (MCP-1/CCL2), interleukin 1 (IL-1) [43-47]. Evidence suggests that all of those molecules may act on immune cells leading to local and generalized inflammation and may also affect vascular (endothelial) function by modulating vascular nitric oxide (NO) and superoxide release and mediating obesity related vascular disorders including atherosclerosis and insulin resistance (IR) [34, 46, 48]. Thus, adipose tissue – it is no longer considered just an energy storage organ, but a real endocrine organ, hormones of which have not yet been fully characterized [34, 42]. In addition it becomes clear that adipose tissue is also, if not predominantly, an immune organ, and obesity related diseases like hypertension or atherosclerosis are in fact – immune disorders [34].

Also, one has to remember about other molecules involved in obesity, which are important in appetite control and adipocytes metabolism, which do not *per se* seem to originate from adipose tissue. There is also growing evidence suggesting that the development of obesity-related disturbances may be closely associated with gastrointestinal (GI) tract-derived hormonal dysregulation and chronic inflammation [27, 49-52]. One of such peptide is ghrelin, linking GI tract and satiety regulation to vascular function [34, 53], particularly that it is released in response to certain immune related stimuli [34, 54].

Ghrelin is a hormone which plays a very important role in the development of obesity and IR [25]. Among all discovered orexigenic peptide, ghrelin has been found to be the most powerful [20]. Ghrelin is the only known circulating orexigenic hormone that promotes adiposity [55]. Ghrelin is closely associated to energy homeostasis, weight regulation and obesity [56-61].

Ghrelin is produced primarily in GI organs in response to hunger and circulates in the blood, serving as a peripheral signal telling the central nervous system to stimulate feeding. Ghrelin plasma levels are mainly regulated by nutritional and metabolic factors; in fact they are increased by energy restriction and decreased by food intake and overfeeding [62, 63]. Chronic intracerebroventricular injection of ghrelin increases cumulative food intake and decreases energy expenditure, resulting in body weight gain.

Circulating plasma ghrelin levels are reportedly inversely associated with Body mass index (BMI) in humans [64-67]. It has been observed in several studies that obese individuals have lower circulating levels of ghrelin than non-obese individuals [26, 68] of same age and sex [69]. Furthermore, In humans, ghrelin secretion is decreased in obesity and is normalized following weight loss [60, 69, 70]. All forms of human obesity have inappropriately low ghrelin levels [63].

Exogenous administration of ghrelin is known to acutely increase food intake and chronic treatment greatly enhances body fat in rodents [56, 62]. When ghrelin is injected into the cerebral ventricles of rats, but also intravenously and subcutaneously, their food intake is potently stimulated [20, 56, 58, 59, 71-73]. These data indicate that ghrelin secretin in obesity is inhibited and it has been assumed that it may reflect a physiological adaptation to the positive energy balance associated with obesity [20, 69]. Careful prospective clinical studies during weight loss or weight gain are now needed to further clarify the role of the recently discovered hormone ghrelin in the pathogenesis of human obesity [69]. In addition, the role of hormones involved in energy homeostasis in CVS is still poorly understood.

It has been shown that low ghrelin concentrations is associated with IR [68, 74-76]. In addition, recent literature suggests that besides food intake and energy balance, ghrelin also

controls glucose metabolism [77]. Furthermore, among obese subjects, plasma ghrelin levels are lower in IR persons compared to insulin sensitive persons [25, 78]. There is increasing amount of evidence that also ghrelin may have an important role in modulating function of adipose tissue [25].

Considering that obesity has a significant role in modulation of the ghrelin expression, it is very important to know how ghrelin is involved in the regulation of adipocyte metabolism [25]. Several studies have suggested that ghrelin may play an important role in adipogenesis and storage of energy in adipose tissue [25, 56, 79, 80].

Kim *et al.* have shown that ghrelin has a direct mitogenic effect on 3T3-L1 preadipocytes [80]. The minimum effective concentration of ghrelin observed in these experiments was comparable to the circulating concentration in humans [26, 69], suggesting that, at physiological concentrations, ghrelin can act as an adipocyte mitogen [80]. In addition, Choi *et al*. find that ghrelin stimulated adipocyte differentiation in primary cultured rat adipocytes [81]. In visceral adipose tissue, ghrelin is shown to stimulate lipid accumulation by enhancing the expression of adipogenic genes including peroxisome proliferator-activated receptor gamma (PPAR)-γ, sterol regulatory element-binding protein (SREBP)-1, acetyl-CoA carboxylase, fatty acid synthase lipoprotein lipase, perilipin, adipocyte determination and differentiation-dependent factor (ADD)1, and adipose protein 2/fatty acid binding protein (aP2) during adipocyte differentiation [25, 79, 80]. It is possible that these functions are mediated *via* AMP-activated protein kinase (AMPK) pathway [25, 82]. It has been also demonstrated that infusion of ghrelin modulates adipocyte metabolism by inhibiting isoproterenol induced lipolysis [83], regulating adipogenesis [84, 85], suppressing noradrenalin release in brown adipose tissue [86], and promoting glucose and triglyceride uptake and antiapoptotic actions [25, 80, 85]. Ghrelin has been also shown to

stimulate lipogenesis and to inhibit lipid oxidation in white adipocytes, whereas in brown adipocytes central ghrelin infusion results in decreased expression of uncoupling proteins, molecules contributing to energy dissipation [25, 85]. All of thesefindings strongly support the view that ghrelin may have an “energy saving” elects on adipose tissue [25]. In addition, ghrelin has also been shown to directly promote bone marrow adipogenesis *in vivo* [25, 85, 87]. However, Zang et al. have recently shown that ectopic overexpression of ghrelin gene in 3T3-L1 cells promoted adipocyte proliferation but inhibited adipogenesis by stimulating cell proliferation [80, 87].

Ghrelin has been demonstrated to interact with triglyceride-rich lipoproteins, HDL, very high-density lipoproteins, and to some extent with LDL [88, 89]. In population studies, plasma ghrelin concentrations have also been found to associate positively to HDL cholesterol levels and LDL particle size and negatively with LDL and triglyceride concentrations [90-93].

Genetic variations in ghrelin and ghrelin receptor gene have been demonstrated to play a role in the determination of plasma levels of HDL-cholesterol in some populations, but this finding has not been duplicated in all populations [67, 94-96]. In addition, a contradictory positive association between plasma ghrelin levels and plasma LDL cholesterol has been found [97]. Recent investigations have demonstrated that ghrelin administration in rats can induce tissue-specific changes in the expression of genes associated with mitochondrial and lipid metabolism and it can cause triglyceride deposition in the liver in preference to the skeletal muscle [98]. These interesting findings suggest that ghrelin indeed has a role in lipid metabolism. Further studies investigating the direct effect of ghrelin on lipid metabolism are definitely warranted. Thus, that ghrelin has proatherogenic alterations should be linked to involvement of ghrelin in obesity and atherosclerosis.

3. Ghrelin and atherosclerosis

Atherosclerosis is a chronic inflammatory disease that predisposes to CAD, stroke and peripheral arterial disease, responsible for most of the cardiovascular morbidity and mortality [99, 100]. It is an inflammatory process, triggered by the presence of lipids in the vascular wall, and encompasses a complex interaction among inflammatory cells, vascular elements, and lipoproteins through expression of several adhesion molecules and cytokines [4, 100]. Inflammation plays an important role in the pathogenesis of atherosclerosis [101]. Epidemiologic studies have identified environmental (stress, smoking, etc.) and genetic (dyslipidemia, type 2 diabetes mellitus (T2DM), IR, and hypertension) risk factors predisposing to atherosclerosis [99]. Atherosclerosis is initiated by an accumulation of lipids, necrotic cells and fibrous elements in the neointima of medium and large arteries [102]. The major cells that contribute to atherosclerotic lesion formation are the endothelial cells (EC), vascular smooth muscle cells (VSMC) and macrophages [103-105]. The endothelium forms a permeable barrier between the blood and the vascular subendothelial space [99]. Whenever mechanical or chemical effectors weaken this barrier, a response is initiated [99]. Such activated EC produce several molecules which promote monocyte transmigration and subsequent differentiation in macrophages in the subendothelial space [102]. These events occur at the early stages of atherosclerosis [102]. Subsequently, VSMC proliferate and produce extracellular matrix components [106]. The activation of VSMC results in the release of pro-inflammatory cytokines, which, combined with the secretion of matrix metalloproteinases (MMP) and expression of pro-coagulant factors, results in a chronic inflammation [106]. Atherosclerosis progresses to a pathologic condition when this clearance pathway becomes inefficient, and the presence of a large lipid core in the

atherosclerotic lesion correlates with the severity of the pathology [99]. Key features of rupture-prone unstable plaques are a thinned fibrous cap overlying a large necrotic core in the setting of an active inflammatory infiltrate [107]. Atherosclerotic plaque rupture is caused by a combination of plaque biomechanical forces that are dependent on the fibrous cap thickness, necrotic core thickness, and the extent of positive coronary arterial remodeling [100, 108].

It has been shown that ghrelin may have and important role in cardiovascular function, including regulation of atherosclerosis [22]. One study showed that the plasma concentration of ghrelin had a positive correlation with development of carotid artery atherosclerosis in males, but not in females [22, 109]. Animal studies suggest that ghrelin receptors were significantly up-regulated (3-4 fold) in both atherosclerotic coronary arteries and saphenous vein grafts with advanced intimal thickening, when compared with normal vessels [110, 111]. However, a research on kidney transplant patients demonstrates that lower plasma ghrelin concentration is an independent marker for abnormalities in glucose homeostasis, which is related to greater carotid intima-media thickness (cIMT) [112], a well-established surrogate marker for atherosclerosis. Furthermore, findings in older subjects with metabolic syndrome (MS) demonstrate that cIMT is significantly inversely correlated with ghrelin levels [113] and in elderly hypertensives des-acyl ghrelin had a significant inverse correlation with cIMT [22, 114]. The effects of ghrelin on increased cIMT, which is a surrogate marker to the development of atherosclerosis, remain to be fully elucidated [113]. The study done by Kotani et al. suggests that ghrelin might play a role in increased cIMT, independently with age and systolic blood pressure (BP), in older subjects with MS [113]. Positive associations between cIMT and both age and BP in this study are basically consistent with prior findings of studies on MS [113, 115, 116]. Further research with a

perspective design and a larger sample size is needed to clarify the causal role of ghrelin in carotid atherosclerosis [113].

On the whole, ghrelin and its receptors participate in the occurrence and development of the atherosclerotic process, and elevations of both levels may represent a compensatory mechanism to reverse the process, while, in kidney transplant patients and older people with MS or hypertension, this compensatory ability may be lost or damaged, of course, this deduction need further confirmation [22]. So far, the potential regulating mechanism of ghrelin on atherosclerosis is not clear [22].

Endothelial dysfunction is considered to be one of the earliest events of the atherosclerotic development. In patients with endothelial dysfunction, plasma ghrelin level decreases [22, 117]; conversely, the application of exogenous ghrelin can improve endothelial dysfunction in MS patients by increasing NO bioactivity [118]. In addition, atherosclerosis is linked to inflammation and immunological reaction [22]. Studies found that, ghrelin can inhibit proinflammatory cytokine pro-duction, mononuclear cell binding, and nuclear factor-kappa B (NF-κB) activation in human endothelial cells *in vitro* as well as endotoxin induced cytokine production *in vivo* [119], moreover, exogenous ghrelin may significantly inhibit TNF-α/ interferon-γ-induced CD40 expression in human umbilical vein EC (HUVEC) cells in a concentration-dependent manner [22, 120].

Ghrelin inhibits proinflammatory cytokine production, mononuclear cell binding, and NF-κB activation in human endothelial cells *in vitro* and endotoxin-induced cytokine production *in vivo* [119]. These novel antiinflammatory actions of ghrelin suggest that the peptide could play a modulatory role in atherosclerosis, especially in obese patients, in whom ghrelin levels are reduced [119]. In the recent study, reported by authors examined the effects of ghrelin on

inflammatory responses in cultured HUVECs and *in vivo* after endotoxin administration [119]. Their findings provide the first evidence that ghrelin acts as an antiinflammatory peptide in the cardiovascular system [119]. Li et al. demonstrate for the first time that ghrelin has potent antiinflammatory effects in HUVECs, likely mediated by inhibition of NF-κB activation [119]. Ghrelin also inhibited endotoxin-induced systemic cytokine production *in vivo* [119]. Findings reported by the same authors may help to explain the beneficial effects of ghrelin administration in various pathological states associated with inflammation, including experimental models of heart failure and septic shock [119]. Moreover, their findings suggest that a reduction in endogenous ghrelin could contribute to the increased incidence of atherosclerosis in patients with obesity [119].

Since ghrelin is an effective vasodilator [109, 121], it has been suggested that the change in the receptor density might reflect the beneficial role of ghrelin in human atherosclerosis [109, 110]. On the other hand, a recent study has demonstrated nonbeneficial vasoconstrictive actions of ghrelin [122]. To clarify these contrasting findings, Poykko et al. characterized the association between ghrelin concentrations and atherosclerosis in humans [109]. The major finding of their study was that plasma ghrelin concentrations associated positively with the degree of subclinical atherosclerosis [109]. First, the beneficial haemodynamic effect and vasoactive role of ghrelin has been demonstrated both *in vitro* [121] and *in vivo* [123] as well as in association studies [68, 109]. Western blot analysis demonstrated that treatment with ghrelin increased endothelial NO synthase (eNOS) expression in the aorta of GH-deficient rats [33]. Furthermore, it has been reported that administration of ghrelin improves endothelial dysfunction and increases eNOS expression in rats through GH-independent mechanisms [33, 124]. Administration of ghrelin may be a new therapeutic approach to the treatment of endothelial impairment and may contribute to

the prevention of atherosclerosis [33]. Low ghrelin concentrations have been associated with metabolic disturbances such as IR, T2DM, and MS [68, 109], which are commonly recognized as risk factors of atherosclerosis [109]. Data indicate that although reductions of both plasma desacyl ghrelin and plasma high-molecular weight (HMW) adiponectin are associated with obesity, only the former is a useful cardiometabolic marker for predicting atherosclerosis in elderly hypertensives [114]. Although therewas a significant association between the des-acyl ghrelin and NO levels, the association of des-acyl ghrelin with atherosclerosis appears to be independent of the NO level [114].

Recent data document that ghrelin inhibits angiotensin II (Ang II) induced contraction and proliferation in human aortic smooth muscle cells (HASMC), and thus it is involved in VSMC regulation [125]. In the vascular system, binding sites are present in aorta, peripheral arteries and veins, and their density is increased in atherosclerosis and in the atheromasic plaque [111, 125]. In addition, ghrelin was reported to lower blood pressure *in vivo* by inducing vasodilatation of resistance vessels [126]. Recent data, reported by Rossi et al. show that ghrelin affects Ang II-induced contraction of HASMC, and that this inhibition is mediated by ghrelin binding to a specific receptor and subsequent activation of the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway [125]. Findings are consistent with the vasodilatory effect reported *in vivo* by Okumura et al. [127] and document for the first time the relaxing effect exerted by ghrelin on HASMC, and suggest that it is mediated by cAMP/PKA pathway activation [125]. In addition Rossi et al. showed that ghrelin, *per se*, did not affect HASMC proliferation, but it showed the capability to antagonize Ang II-induced HASMC proliferation, in a dose-dependent manner and *via* GHS-R1a receptor [125]. The antiproliferative effect seems to be mainly mediated by the cAMP pathway [125]. This is consistent with cAMP pathway

activation being documented to inhibit proliferation induced by Ang II and several other agonists, which is mediated by protein kinase C (PKC), extracellular-signal-regulated kinase (ERK 1/2) and protein kinase B (Akt) [128-130]. This data document that ghrelin affects several HASMC functions, opening the way to consider ghrelin as a possible therapeutic target in many pathological conditions associated with vascular damage and remodeling, and not only in those associated with decreased circulating ghrelin levels [125].

4. Conclusion

The literature facts that we have taken into consideration, as well as our published and preliminary results, relating to protective effects of ghrelin on CVS, suggest that ghrelin could be one of the essential therapeutic molecules in the treatment of cardiac dysfunction and disease. Future investigations should now focus on the mechanisms of ghrelin actions which might present new approaches involved in the antiatherosclerotic effects revealed in this chapter. Thus, ghrelin may become a new therapeutic target for the treatment of some CVD. It is therefore of great importance to understand molecular mechanisms, which represent the foundation of ghrelin effects on CVS, both in physiological, and pathophysiological states. Further studies are necessary to investigate the potential mechanisms for the effects of ghrelin on CVS. Elucidation of the precise mechanism by which ghrelin regulates atherosclerosis may provide key insights into ghrelin's administration in atherosclerosis therapy [22].

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