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# The Relationship Between Chronic Alcohol Use and Type 2 Diabetes Mellitus: New Insights into Mechanisms of Appetite-Regulating Peptides

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## 1. Introduction

Appetite regulating peptides, particularly ghrelin and leptin in alcohol dependence are significantly related with abnormal glucose tolerance or insulin resistance which contribute to Type 2 diabetes mellitus (T2DM) [1-5]. Available evidence consistently indicates that altered levels of ghrelin and leptin are linked to overall diabetogenic effects of chronic alcohol consumption, and have important mediating roles in the deteriorated pathophysiology of T2DM in alcoholic patients [6]. Moreover, these peptides in the regulation of food seeking behavior have a similar mechanism of controlling of alcohol craving behavior [7, 8]. Therefore, alterations of the peptides modulating numerous metabolic processes could present an intriguing biological mechanism on the relationship between chronic alcohol consumption and risk of T2DM. However, the manner in which the peptides contribute to the development or maintenance of T2DM with alcohol dependence is not clear. This review describes ghrelin and leptin implicated in the elevated risk of developing T2DM with chronic use of alcohol that attributes to the impact of glucose and insulin metabolism. Additionally, to identify whether these two peptides are relevant to the increase in the clustering of metabolic disturbance and progression of T2DM, the background information on the peptides, their role in glucose homeostasis and insulin function in addition to their mechanism of action are discussed. This review on the relationship between chronic use of alcohol and T2DM may further clarify the role of the peptides and provides an insight into the effects of chronic alcohol use in the pathophysiology of T2DM.

## 2. Pathophysiology of T2DM

T2DM, known as “non-insulin-dependent DM,” is a complex, multifactorial metabolic disorder. Characteristic features of T2DM include chronic hyperglycemia and declining

pancreatic  $\beta$ -cell effectiveness, leading to the absence of a first-phase insulin response to nutrient ingestion. Further, slower glucose absorption and higher fasting glucose levels occur from factors such as a reduced insulin-mediated glucose uptake in muscle, impaired hepatic insulin sensitivity, defective insulin action and/or secretion in liver and a disruption of secretory function of adipocytes [9-11]. Glucose levels rise and hyperglycemia develops from deteriorated insulin secretion [12]. Mechanistically, the manifestation of T2DM features a relative decrease in insulin secretion suggesting that this may be in accordance with a decreased  $\beta$ -cell mass failing to compensate for peripheral insulin resistance [13-16]. In the last two decades, declining pancreatic  $\beta$ -cell effectiveness has been a criterion for the development of hyperglycemia and T2DM; its progressive character also determines the course of the disease [17]. Impaired glucose-stimulated insulin secretion, defective  $\beta$ -cell gene expression and disrupted mitochondrial ultrastructure is thought to be due to lipid accumulation and 'lipoapoptosis' is observed in pancreatic  $\beta$ -cells from type 2 diabetic animals [18]. This is also supported by reports that chronic, high glucose administration generates the combination of hyperglycemia and chronic dislipidemia, termed 'glucolipotoxicity,' driving a vicious cycle by which metabolic abnormalities impair insulin secretion, which further aggravates metabolic disturbances in  $\beta$ -cell lines and isolated rat islets [19].

There is mounting evidence that chronically elevated circulating levels of glucose and fatty acids, critical characteristics of T2DM, contribute to relentless  $\beta$ -cell function decline, by endorsing glucolipotoxicity, which induces endoplasmic reticulum (ER) stress [20, 21], oxidative stress [22, 23], mitochondrial dysfunction [23, 24] and islet inflammation [25, 26]. Several studies have provided evidence that prolonged exposure to increased concentrations of fatty acids is associated with reduction of glucose induced insulin secretion [27], impairment of insulin gene expression [28, 29] and induction of  $\beta$ -cells death [30, 31]. Importantly, lipoapoptosis only occurs in the presence of concomitant elevation in insulin secretion [32, 33]. Thus, hyperglycemia and hyperlipidemia have been postulated to conduct to the worsening of insulin secretory capacity and  $\beta$ -cell mass observed in T2DM [16]. It is to note, that during feeding, insulin secretion occurs in two phases. An elevation of insulin synthesis in pancreatic  $\beta$ -cells following an initial rapid release of insulin (i.e. first phase) to nutrient ingestion occurs primarily in response to elevated circulating glucose concentrations. The insulin level stimulates glucose uptake into striated muscle tissues through glucose transport type 4 (GLUT-4) for utilization as a source of energy and into adipose tissues for glycerol synthesis; it also affects liver cells thereby activating glycogen formation. Consequently, glucose utilization by these different tissues contributes to a decrease in concentrations of glucose in blood. Long term release of insulin occurs in response to continuously high glucose concentrations as part of the second phase of insulin response. On the other hand, during this period of hypoglycemia there is an altered interaction between pancreatic islets and glucagon-producing  $\alpha$  cells, causing increased plasma glucagon, and residual  $\beta$ -cell function largely preserves the first-line defence against hypoglycemia in T2DM [34].

### 3. Interplay between alcohol consumption and T2DM

Chronic, heavy alcohol consumption, an independent risk factor for T2DM [35-37], disrupts glucose homeostasis and is associated with development of insulin resistance [38-40].

#### 3.1. Epidemiological evidence

The association between alcohol consumption and DM was demonstrated early in 1971 by Phillips et al. [41]. This study suggested that alcohol with doses of 266 to 513 ml produced glucose intolerance and insulin resistance in three of six healthy subjects. Later, this relationship was also demonstrated in a cross-sectional health screening survey of 636 individuals with negative urine glucose, suggesting that alcohol dependence was one of the malignant factors in individuals with impaired glucose tolerance diagnosed by performing a 75-g oral glucose tolerance test (OGTT) [42]. Moreover, alcohol consumption influenced fasting plasma glucose levels along with obesity after analysis of 434 pairs of adult female nondiabetic twins [43]. These results implied that alcohol might impair fasting and postprandial glycemic controls and thus may be a risk factor for T2DM, sharing common genetic factors. Indeed, alcohol consumption within the past week appears to be an independent risk factor of the development of T2DM after a 10 year, prospective population-based study [44]. This significant association was observed only in men and remained significant after adjusting for other hazards of T2DM.

However, there also have been studies with negative or opposite findings explaining the relationship between alcohol consumption and the development of T2DM. Alcohol consumptions of 5-14.9g/d and more than 15g/d were associated with a decreased relative risk of DM in women [45]. In a later study worked on younger women, light to moderate drinking (<14.9g/d) was also associated with a lower risk of T2DM compared to lifelong abstinence, whereas heavy drinking showed a significantly increased diabetic risk [46]. Similarly, moderate amount of alcohol consumption (30.0-49.9 g/d) was associated with reduced risk of the development of DM in 41,810 male health professionals [47]. Lowering the incidence of T2DM by light to moderate drinking, T2DM was also observed in older adults [48]. On the other hand, no effect of alcohol consumption on the development of T2DM was reported in large population-based survey [49]. The aforementioned results suggest the presence of possible influencing factors, such as gender [44, 50] and amount of alcohol consumption [46, 50].

Regarding drinking patterns, Conigrave et al. [51] found that more frequent drinking is more protective against T2DM. A later study [50] also showed that binge drinking for 1-3 days increased the risk of T2DM compared to non-drinking, while drinking the same amount over a week did not increase the risk. Meanwhile, there has been controversy on the type of alcoholic beverage and the risk of T2DM. Some studies noted protective effects of wine on T2DM than other alcoholic beverages [52]. However, other studies presented no significant difference with various alcoholic liquors [48, 51]. In addition, obesity may also influence the relationship between alcohol consumption and T2DM. A systematic review of studies in Japanese showed that alcohol consumption is a risk factor for DM, whereas

moderate drinking is associated with a reduced diabetic risk in higher body mass index (BMI) men in some studies [53]. Although the mediating effects of obesity are supported by a positive association between alcohol intake, adiponectin levels and insulin sensitivity [54, 55], more studies will be needed to confirm this issue.

To date, 3 meta-analyses were performed in an attempt to draw a possible conclusion. Carlson et al. [56] analyzed data from 13 cohorts and suggested a U-shaped relationship between the amount of alcohol consumption and risk of T2DM. Moderate drinking, corresponding to about 5-30g/d was associated with a reduced risk of DM (relative risk: RR=0.72, 95% CI=0.67-0.77) in both men and women. This U-shaped relationship in both sexes was also demonstrated in a meta-analysis by Koppes et al. [57] in which lowest risk was in alcohol drinkers of 6-48g/d. Drinkers of  $\geq 48$ g/d showed equal RR to that of nondrinkers. In their study, adjustment for confounding factors including diagnostic measures of T2DM (self-reported versus tested) and BMI (low- versus high-BMI) was performed. Results of a self-reported diagnosis were associated with lower RR than using a diagnostic test, whereas BMI did not affect the RR of T2DM. A third meta-analysis of Bauliunas et al. [58] additionally identified a deleterious effect of heavy drinking ( $\geq 60$  g/d for men and  $\geq 50$ g/d for women) in addition to the protective effect of moderate drinking in both sexes.

### 3.2. Alcohol consumption and risk of T2DM

Along with the epidemiological data on the relationship between alcohol consumption and T2DM, studies exploring underlying mechanisms between them have been performed. Most directly, alcohol can induce acute and chronic pancreatitis and result in DM as in T1DM [59]. However, there is a growing body of evidence suggesting that the diabetogenic effect of alcohol does not seem to be mediated by decreased insulin secretion [41]. The priming effect of ethanol-enhanced insulin secretion in pancreatic  $\beta$ -cells might be caused by an early defence mechanism used to compensate for alcohol-inhibited basal insulin secretion. In contrast, a limited number of studies have reported deleterious effects of alcohol on  $\beta$ -cells in which alcohol inhibited insulin secretion [60].

Excessive heavy alcohol use increases ROS production and may be a mechanism of pancreatic  $\beta$ -cells dysfunction in T2DM. The reason is that ROS production is one of the earliest events in glucose intolerance through mitochondrial dysfunction and  $\beta$ -cells are very sensitive to oxidative stress [61]. Previous studies of alcohol dependence have shown that alcohol elevated the level of  $\beta$ -cell apoptosis and increased insulin resistance in the liver and skeletal muscle, which is among the earliest detectable alterations in humans with T2DM [62]. In addition, the mechanisms by which this occurs are often multifactorial and quite complex, involving many cell signaling pathways. A common result of DM is hyperglycemia, which in turn contributes to the progression and maintenance of an overall oxidative environment [63]. In obesity, oxidative stress is now recognized to be an important feature in dysregulation of adipokines and inflammation [64].



Among potential mediators of alcohol-induced insulin resistance including acetate, lactate, acetaldehyde, free fatty acids and triglycerides, hepatic insulin sensitizing substance (HISS) and glutathione need to be considered. Alcohol suppresses the release or action of HISS and meal-induced insulin sensitization in rats [65]. Moreover, in animal models, acute alcohol administration also reduces glutathione [66] which is important for HISS release [67]. As with acute alcohol consumption, hepatic glutathione and HISS seem to be involved. In contrast to the acute alcohol effect, chronic ethanol consumption increased hepatic glutathione levels and HISS release in cases of moderate dose, whereas decreased glutathione and HISS were reported at high doses [68].

On the other hand, results on the effect of chronic ethanol consumption on insulin sensitivity showed that insulin sensitivity was improved [66, 69-72] or unchanged [73-75] after chronic alcohol consumption. The mechanism by which chronic alcohol consumption enhances insulin sensitivity also remains elusive. Alcohol consumption is proposed to increase plasma adiponectin levels, which subsequently lowers plasma TNF- $\alpha$ , which interferes with insulin signaling [76]. Taken together, alcohol might induce alterations in insulin resistance mediated by lipids, inflammation oxidative stress and altered metabolism. Moreover, the effect of alcohol on insulin sensitivity may be influenced by periods of and amount of alcohol consumption. Impaired suppression of hepatic glucose production by insulin is likely due to impaired insulin signaling in liver after chronic alcohol exposure. For instance, chronic ethanol consumption decreases tyrosine phosphorylation of insulin receptor substrate-1 as well as activities of PI 3-kinase and Akt (protein kinase B) in the liver [77].

### 3.3. Ghrelin and leptin correlated with risk of T2DM in alcoholic patients

It has been investigated that ghrelin may be associated with  $\beta$ -cell hypofunction and the first-phase insulin secretion defects in T2DM and exert to regulate glucose homeostasis with glucagon and insulin [78]. Additionally, abnormal glucose tolerance and insulin resistance, which are main characteristics of T2DM, through performing 75g OGTT seemed to be affected by leptin as well as, the levels of leptin were higher in diabetic patients independently of body fat mass when it compared with healthy control patients [4]. Thus, ghrelin and leptin have been regarded to have influence on T2DM. Valuable efficacy of plasma ghrelin and leptin levels by the development of T2DM in patients with alcohol dependence were changed [6]. The data showed that ghrelin levels did not differ among the groups, even though there was a tendency towards decreased ghrelin levels; whereas the leptin level increased significantly with development of T2DM (Fig. 1).

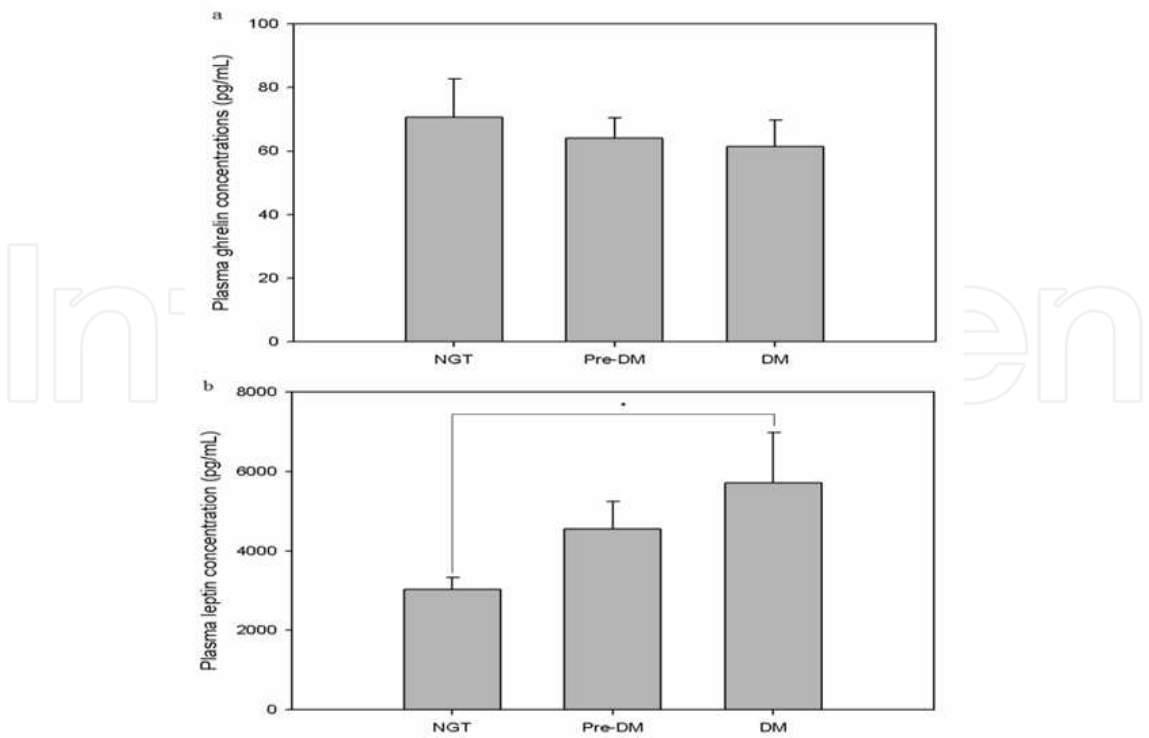
The demographic characteristics of each group were shown in Table 1. The three groups exhibited similar values of age, height, weight, BMI and lipid profiles such as HDL-cholesterol, LDL-cholesterol, and triglyceride. Fasting glucose concentration and hemoglobin A1c, HOMA-IR in the DM group had significantly higher levels than NGT and Pre-DM groups.

Clinical characteristics	NGT	Pre-DM	DM
<i>Alcohol history</i>			
Alcohol use disorder identification test	21.7 ± 1.09	21.17 ± 1.61	24.3 ± 1.23
Alcohol dependency scale	42.29 ± 1.38	38.86 ± 1.74	43.83 ± 1.79
Onset age of problematic drinking (years)	36.58 ± 1.89	37.56 ± 1.68	40.05 ± 2.88
<i>General characteristics</i>			
Age (years)	47.35 ± 1.37	48.87 ± 1.57	52.77 ± 1.84
Weight (kg)	66.83 ± 1.46	65.39 ± 1.25	63.96 ± 1.92
Height (cm)	169.57 ± 0.81	167.76 ± 0.8	167.38 ± 0.85
BMI (kg/m <sup>2</sup> )	23.19 ± 0.42	23.2 ± 0.36	22.77 ± 0.57
HDL-Cholesterol (mg/dl)	56.91 ± 2.27	51.08 ± 2.36	55.19 ± 4.44
LDL-Cholesterol (mg/dl)	113.09 ± 3.87	104.63 ± 4.95	101.96 ± 4.72
Triglyceride (mg/dl)	115.02 ± 10.31	135.33 ± 13.06	139.88 ± 15.54
GOT (IU/l)	69.5 ± 11.53	71.7 ± 9.19	52.54 ± 6.96
GPT (IU/l)	40.93 ± 5.25	50.07 ± 8.66	34 ± 6.19
γ-GTP (IU/l)	178.87 ± 45.33	205.07 ± 32.64	254.96 ± 67.99
<i>Clinical characteristics related to glucose tolerance</i>			
Fasting Glucose (mg/dl)	86.09 ± 1.05	91.48 ± 1.45	124.19 ± 7.01**
Fasting Insulin (μU/ml)	4.8 ± 0.84	4.73 ± 0.69	6.22 ± 1.4
HemoglobinA1c (%Hb A1c)	5.5 ± 0.05	5.64 ± 0.08	7.13 ± 0.36**
HOMA-IR	1.02 ± 0.17	1.05 ± 0.15	1.87 ± 0.36*
HOMA-β	83.56 ± 18.56	66.13 ± 11.55	54.91 ± 14.87

**Table 1.** Characteristics of subjects classified by oral glucose tolerance test among patients with alcohol dependence BMI, body mass index; HDL-cholesterol, high density lipoprotein-cholesterol; LDL-cholesterol, low density lipoprotein-cholesterol; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; γ-GTP, γ-glutamyl transferase; HOMA-IR, homeostasis model assessment-insulin resistance; HOMA-β, homeostasis model assessment-β-cell function (\*, p<0.05 and \*\*, p<0.01 compared with NGT).

Moreover, this study demonstrated that leptin was significantly correlated with BMI, fasting insulin concentration and HOMA-IR reflecting insulin resistance (Table 2). The BMI was similar in the groups and the subjects were regarded as a non-obese group. The leptin produced by adipocytes increased in proportion to fat mass [79, 80]. The plasma leptin levels are highly correlated with BMI in both obese and normal weight subjects [81]. In spite of the correlation between BMI and leptin, covarying for BMI in our statistical analyses did not alter our findings.

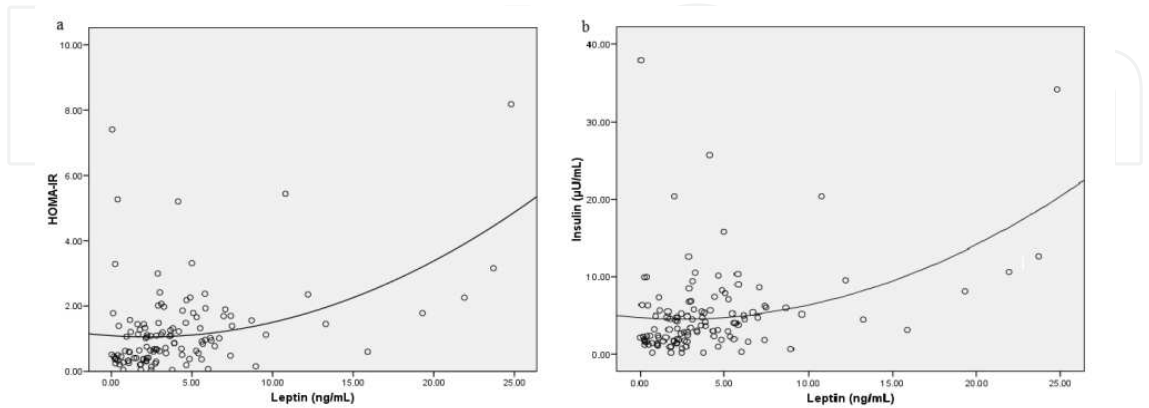
Leptin also has been shown to be correlated with insulin concentration and insulin sensitivity [82-84]. The direct relationship between leptin and insulin seemed to be mutual. Insulin also had a role in the regulation of leptin concentrations [85]. Among all patients with chronic alcoholism, significant quadratic association of leptin level with insulin concentration and HOMA-IR were observed using simple regression analysis (Fig. 2, Table 3).



**Figure 1.** Comparison of plasma (a) ghrelin and (b) leptin levels among three groups classified by oral glucose tolerance test (OGTT) among alcoholic patients (\*,  $p<0.05$  compared with NGT).

	BMI	Insulin	Leptin	Ghrelin	HOMA-IR
BMI					
Insulin	0.17				
Leptin	0.334**	0.379**			
Ghrelin	-0.066	-0.168	-0.171*		
HOMA-IR	0.195*	0.960**	0.388**	-0.173	

**Table 2.** Correlation of BMI, fasting insulin, leptin and ghrelin levels and HOMA-IR (\*,  $p<0.05$  and \*\*,  $p<0.01$ ).



**Figure 2.** Quadratic regression plots of plasma leptin levels with both insulin resistance index (a) and fasting insulin level (b) in chronic alcoholic subjects. The quadratic regression equation was  $y = 0.007x^2 - 0.037x + 1.075$  for fasting leptin level and HOMA-IR (A) and  $y = 0.031x^2 - 0.141x + 4.509$  for fasting leptin and insulin level (B).



Independent-Dependent	Linear	Quadratic
Leptin-HOMA-IR	0.390**	0.437**
Lepin-Insulin	0.363**	0.409**

**Table 3.** Comparison of various kinds of regression models to find better model to fit the relationship of leptin with HOMA-IR and insulin level (\*\*,  $p < 0.01$ ).

In conclusion, leptin can play a role in the pathogenesis of T2DM in patients with alcohol dependence. Chronic alcohol consumption might produce leptin resistance, which produces a significant correlation between leptin and the fasting insulin concentration,  $\beta$ -cell function and insulin resistance. However, more study will be needed to determine the mechanism of the relationship between alcohol intake and leptin resistance.

#### 4. Role of the appetite regulating peptides in alcohol dependence and prevalence of T2DM

The neuropeptide, ghrelin secreted from cells of the gastric oxyntic glands in stomach, and leptin excreted from white adipose cells, have received attention due their roles in the neurobiology of alcohol dependence [2, 6]. Many studies have suggested that ghrelin and leptin predominantly produce variations of glucose and insulin concentrations, which may initiate metabolic disorders [86, 87]. In addition, recent research regarding neuroendocrinological alterations of ghrelin and leptin in patients with alcohol dependence has showed that chronic use of alcohol represents a potentially crucial risk factor for T2DM prevalence as ghrelin reduces insulin secretion stimulated by the increased level of blood glucose in the  $\beta$  cells of pancreas, while in contrast, leptin increases insulin secretion and action [88-90]. In regards to the diabetogenic effects of chronic use of alcohol, development of pancreatic  $\beta$ -cell dysfunction, insulin resistance, obesity, impairment of liver function in glucose metabolism have been noted [35]. Indeed, alcoholic patients with T2DM have repeatedly been found to have deregulation of the ghrelin and leptin systems, as indicated by impaired insulin secretion, increased hepatic glucose production and decreased peripheral glucose utilization [38-40]. Moreover, these peptides are regarded to have an influence on T2DM-mediated alcohol cravings and relapses in alcoholism during alcohol abstinence [91-94]. Therefore, it is conceivable that alterations of appetite peptides provoked by chronic alcohol use might contribute to the development of T2DM, including defective glucose tolerance and impaired insulin resistance.

The decreases in ghrelin are paralleled by increases in leptin and rises in insulin [87, 95]. Leptin, which is elevated in the plasma of obese subjects, controls fat cell secretary productions on ghrelin secretion due to leptin-related decreases in ghrelin levels. [96-98]. It has been suggested that leptin is significantly associated with BMI and alcohol consumption, influencing fasting insulin concentration and HOMA-IR, and the possible mechanism of alcohol leptin interaction may be attributable to a direct noxious effect of alcohol on the pancreatic islet cells, or may reflect a truncal fat pattern related to heavy use of alcohol [44]. Thus, the adverse effect of heavy use of alcohol on serum insulin

concentrations, a risk for DM, seems to be partially mediated through its effect on BMI. Interestingly, it has been proposed that elevated peripheral insulin resistance may produce increased leptin concentrations regardless of body fat profiles, suggesting that leptin released from fat tissue in alcohol dependence patients may be abundant irrespective of body fat content [6]. Therefore, altered leptin concentrations in alcoholic patients contribute to the incidence of T2DM mainly due to chronic alcohol consumption rather than body fat mass.

In the clinical studies, increases of mean body weights and leptin concentrations resulted from therapeutic treatment of insulin for 1 year in T2DM patients. [99], suggesting that insulin prompted leptin secretion, which was believed to exert influence on the increased body weight. Further, decrease of insulin-stimulated glucose utilization in skeletal muscle was exhibited by long periods of leptin exposure. This is to the fact that insulin-stimulated p38 mitogen-activated protein kinase (MAPK) activation was inhibited and GLUT4 activation was decreased by leptin [100]. Leptin also can interfere with insulin signaling and induce gluconeogenesis in hepatocytes directly [83]. Insulin-stimulated glucose uptake into isolated adipocytes was inhibited by chronic alcohol feeding via vitiation of the fusion of GLUT4 vesicles at the plasma membrane of rats. Chronically fed with alcohol sustains insulin signaling through PI 3-kinase in adipocytes [101] but results in the disruption of insulin mediated Cbl/TC10 signaling pathway which leads to attenuated insulin-stimulated glucose transport [102]. Thus, a combination of decreased GLUT4 expression and impaired insulin-stimulated GLUT4 trafficking to the plasma membrane contributes to reduced glucose uptake in response to insulin in adipocytes. Hence, the possibility that ghrelin and leptin can be related with deteriorated pathophysiology of T2DM, aligned with defective insulin signaling pathway, including change in kinase activity, glucose transporter translocation and intracellular enzyme activity, in alcoholic patients exists.

## 5. Ghrelin in glucose and insulin homeostasis

Ghrelin was originally isolated from the stomach, but ghrelin has also been identified in other peripheral tissues, such as the gastrointestinal tract, pancreas, ovary and adrenal cortex [3, 103-105]. Regulation of ghrelin secretion, as well as its biological effects, appears to be opposite those of leptin and antagonize leptin's effects in appetite regulation [95, 106-108]. A suppressive role of ghrelin in insulin secretion from pancreatic islets is supported by the observation that ghrelin inhibits glucose-stimulated insulin secretion and disrupts glucose tolerance in normal subjects [109]. There is evidence that ghrelin may have proliferative or protective roles on  $\beta$ -cells [110] and stimulates insulin secretion, which primarily occurs in response to increased circulating glucose levels, whereas insulin reduces plasma ghrelin in normal controls and T2DM patients [111]. Moreover, ghrelin may be associated with  $\beta$ -cell hypofunction and first-phase insulin secretion defects in T2DM as well as regulates glucose homeostasis with glucagon and insulin [78]. Furthermore, it has been noted that deficiency of the genes encoding ghrelin and its receptor (GHS-R1a) enhances insulin levels, increases glucose-stimulated insulin secretion, improves peripheral insulin sensitivity and prevents high-fat diets from inducing obesity [112]. Similarly, ghrelin

receptor antagonists which inhibit ghrelin signaling have been shown to improve the diabetic condition by promoting glucose-dependent insulin secretion [113]. Ghrelin can also inhibit the activity of glucose-sensing neurons in the dorsal vagal complex of rats, indicating that ghrelin manipulates the sensitivity of glucose-sensing neurons [114, 115].

The pathophysiological role of ghrelin in glucose homeostasis was strengthened by the fact that ghrelin may decline endogenous glucose production through suppression of insulin secretory capacity [116], while reinforcing insulin action on glucose disposal [112]. A recent study demonstrated that acylated ghrelin has a positive correlation with insulin resistance, as indicated by the increased insulin and glucose concentrations, whereas correlation between des-acylated ghrelin and HOMA-IR was shown to be negative [117]. On the other hand, it has been reported that fasting ghrelin levels at any other point might be impossible to use for predicting the development of impaired glucose regulation [118]. The reduction of ghrelin levels were shown to be associated independently with T2DM, agreeing with the results of studies demonstrating that ghrelin has an inverse correlation with insulin resistance evaluated by HOMA-IR [119]. Moreover, increases in ghrelin during chronic alcohol use suggested that a role of ghrelin may contribute significantly to the overall alcohol response. It has likewise been reported that ghrelin is not only a regulator of glucose and insulin metabolism in the central nervous system (CNS), but also a modulator of those in the periphery. In the periphery, ghrelin has been shown to stimulate hepatic glucose production [120] and inhibit insulin release from pancreatic islets [121, 122]. Peripheral ghrelin produced in the gastrointestinal tract [103, 123] reaches ghrelin-receptors in the anterior pituitary and potentially in the mediobasal and mediolateral hypothalamus through the general circulation to stimulate GH release and to regulate energy homeostasis [124]. Therefore, it can be postulated that decreases in ghrelin concentrations as well as facilitation of the development of perturbations in glucose metabolism resulting from deregulation of the CNS and the periphery might lead to perseverance of T2DM. Besides, low blood ghrelin concentrations appears to influence growth hormone/insulin like growth factor-1-axis which may, in turn, affect increased insulin resistance and ultimately manifest T2DM [125].

## **6. Leptin in glucose and insulin homeostasis**

Leptin, an adipocyte-derived anorexigenic peptide plays a primary role in regulation of energy homeostasis including food intake and energy expenditure involved in obesity, regulating overall metabolism and particularly glucose metabolism. Leptin is transported across the blood brain barrier (BBB) by binding to its receptor in the arcuate nucleus of the hypothalamus to regulate glucose metabolism via central leptin signaling, which modulates sympathetic and neuroendocrine activities [126, 127], as well as through peripheral signaling in insulin-sensitive tissues such as liver and muscle [128, 129]. A previous study demonstrated that serum leptin was positively correlated with fasting blood glucose in obese patients with DM, suggesting that resistance to insulin and leptin may have participated in increasing food intake in T2DM. Additionally, leptin has to be considered as a possible regulator of the gastrophypothalamic axis involved in short-term feeding

regulation [130] and may have a central role in islet cell growth and insulin secretion [131]. In addition, several other appetite-related hormones such as anorexigenic neuropeptides, alpha-melanocyte-stimulating hormone (alpha-MSH), proopiomelanocortin (POMC), cocaine and amphetamine regulated transcript (CART) and corticotropin-releasing hormone (CRH) are stimulated by leptin. Conversely, orexigenic neuropeptides NPY, melanin-concentrating hormone (MCH), orexins and agouti-related peptide (AgRP) are inhibited by leptin which suppresses food intake and enhances energy expenditure through these central interactions, which is associated with T2DM [132-135].

In the brain, obesity and T2DM typified by both insulin and leptin resistance, on account of either reduced BBB transport or impaired neuronal capacity to sense peripheral signals, causes increased concentrations of anorexigenic neuropeptides and reduced concentrations of orexigenic ones [136]. It has been postulated that leptin resistance might be due to defective leptin transport across the BBB [137]. Leptin enters the brain by a saturable transport system and that capacity of leptin transport is lower in obese individuals, thereby providing a mechanism for leptin resistance [138]. The development of leptin resistance most likely involves a period of excess caloric intake, resulting in a disturbance of the leptin system, leading to sustained defects. The hypothalamus exposed to high leptin levels becomes less sensitive to leptin, resulting in a sustained increase in leptin levels [139]. Leptin resistance may also have functional implications in peripheral tissues expressing leptin receptors, such as pancreatic  $\beta$  cells, where insulin is synthesized and secreted; leptin may also affect hepatocytes, muscle and adipose tissue, where insulin exerts its function [140]. In all these tissues, an effect of leptin has been demonstrated on insulin secretion and on insulin-induced activities such as glucose utilization [83, 141]. Also, increased leptin levels, probably reflecting leptin resistance, was shown to be strongly related to insulin resistance [142]. Moreover, peripheral leptin inhibits insulin secretion in pancreatic  $\beta$ -cells [83], whereas insulin stimulates leptin production in adipocytes [85]. Therefore, reciprocal interaction of leptin and insulin called 'adipo-insular axis' is central under physiological conditions.

However, in few studies, glucose and insulin levels were able to increase circulating leptin levels, indicating that the capacity of leptin to suppress insulin secretion in pancreatic  $\beta$ -cell might be a possible involvement of T2DM [143, 144]. Interestingly, reduced leptin sensitivity of the pancreatic  $\beta$ -cell occurs concurrently with hyperinsulinemia resulting from not only decreased insulin sensitivity, but also increased insulin secretion, and consequently hyperleptinemia as part of a vicious cycle that promotes both insulin resistance [145]). Leptin has been shown to increase whole-body glucose utilization, decrease glycogen stores and inhibit insulin-stimulated glucose uptake [146], implying that increased leptin levels contribute to increased glycemia and altered glucose homeostasis [147]. Therefore, the capacity of leptin to suppress insulin secretion in pancreatic  $\beta$ -cell suggests a possible involvement in T2DM. Moreover, obese (*ob*) gene depleted mice exhibited susceptibility to the development of obesity and diabetic disorders, indicating that leptin (an *ob* gene product) induced insulin resistance may be considered a major influence in developing T2DM [148]. Thus, animal models that are used to elucidate mechanisms underlying obesity and T2DM often display an altered diabetogenic imbalance, involving leptin. This suggests

that dysfunction of leptin's ability in T2DM may not only represent a consequence of the disease, but also plays an important role in its cause.

## 7. Inverse interactions between leptin and ghrelin

Leptin is important for the negative feedback regulation of ghrelin in states of moderate body weight increase, whereas recombinant leptin administration is ineffective on altering ghrelin levels in healthy subjects [149]. There is currently evidence that ghrelin and leptin exert antagonistic effects via their specific receptors in the CNS and in peripheral tissues. Ghrelin increases appetite and food intake via centrally mediating actions but, peripherally it modulates pancreatic  $\beta$ -cells function as well as glucose and lipid metabolism [150]. The satiety inducing effects of leptin include the suppression of ghrelin secretion to induce anorexic effects [97]. Adipogenic as well as orexigenic effects of ghrelin are also most likely mediated by a specific central network of neurons that is also mediated by leptin [124, 151-153].

In the brain, ghrelin may transfect the BBB and bind to its receptors in the hypothalamus after secretion into the bloodstream from the stomach [105, 154, 155]. Ghrelin reaches the brain via the vagal nerve and nucleus tractus solitarius [154, 156] and is released locally in the hypothalamus, where it may directly affect various hypothalamic nuclei [154, 157]. In addition, central ghrelin may affect the energy centre in the hypothalamus and both ghrelin and leptin stimulate and suppress, respectively hypothalamic neurons containing various neuropeptides, resulting in anorexic or orexigenic effects on energy balance. Ghrelin thus stimulates the activity of neurons expressing NPY, AgRP and orexin [158-160] and inhibits POMC neurons and CRH-producing neurons [157]. The interaction between ghrelin and leptin in the hypothalamus indicates that these peptides have different effects in the hypothalamic neurons producing various orexigenic and anorexigenic peptides, presenting more or less opposing effects on energy balance.

In hepatocytes, ghrelin reduces and leptin augments insulin signal transduction, resulting in increased and decreased glucose production, respectively [120]. In pancreatic  $\beta$ -cells, insulin release was stimulated by ghrelin but inhibited by leptin administration [3]. Insulin was postulated to act indirectly via ghrelin and leptin to suppress appetite [5]. However, attenuated suppressive action of insulin on ghrelin and particular association between insulin resistance and leptin resistance were shown in T2DM [5, 142]. Thus, leptin seems to be the major determinant of ghrelin effects on progression of metabolic syndromes.

## 8. Conclusion

The studies discussed here demonstrate that the role of appetite regulating peptides, ghrelin and leptin, in alcohol patients with T2DM may be of high importance for clinical research and practice. The extensive functional interactions between these peptides, which may contribute significantly to the overall defecting glucose tolerance with regard to alcoholism, may have a new insight into mechanism of T2DM. Therefore, understanding of mechanisms



underlying the pivotal relations between ghrelin, leptin and glucose homeostasis during chronic use of alcohol represents an additional therapeutic intervention for T2DM.

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