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Alcoholism and Diabetes Mellitus

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Chronic use of alcohol is considered to be a potential risk factor for the incidence of type 2 diabetes mellitus (T2DM), which causes insulin resistance and pancreatic β-cell dysfunction that is a prerequisite for the development of diabetes. However, alcohol consumption in diabetes has been controversial and more detailed information on the diabetogenic impact of alcohol seems warranted. Diabetes, especially T2DM, causes dysregulation of various metabolic processes, which includes a defect in the insulin-mediated glucose function of adipocytes, and an impaired insulin action in the liver. In addition, neurobiological profiles of alcoholism are linked to the effects of a disruption of glucose homeostasis and of insulin resistance, which are affected by altered appetite that regulates the peptides and neurotrophic factors. Since conditions, which precede the onset of diabetes that are associated with alcoholism is one of the crucial public problems, researches in efforts to prevent and treat diabetes with alcohol dependence, receives special clinical interest. Therefore, the purpose of this mini-review is to provide the recent progress and current theories in the interplay between alcoholism and diabetes. Further, the purpose of this study also includes summarizing the pathophysiological mechanisms in the neurobiology of alcoholism.

Keywords: Alcohol; Diabetes mellitus; Glucose; Insulin

INTRODUCTION

Diabetes mellitus (DM) is recognized clinically as a complication of alcoholism, and both alcoholism and DM affect a large population worldwide [1]. Chronic, heavy alcohol consumption, an independent risk factor for type 2 diabetes mellitus (T2DM) [2], disrupts the glucose homeostasis and is associated with development of insulin resistance [3]. However, epidemiological and controlled clinical data on the relationship between the amount of ingested alcohol and the incidence of T2DM have been inconsistent in literature. There is a delicate balance between the harmful effects and the beneficial effects of alcohol on T2DM. While some studies have reported that moderate and sensible alcohol use decreases the risk of T2DM [4] or heavy alcohol use increases the risk of T2DM, with the loss of glycemic control [5], others have suggested that there exists no effects [6]. Whether these effects might be due to gen-

der differences or not, it has been shown with to be inconsistent and the impact of alcohol on pre-diabetes impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) has rarely been investigated [7]. Notably, heavy amounts of alcohol show direct diabetogenic effects with its contribution to excess caloric intake and obesity, induction of pancreatitis, disturbance of the carbohydrate and glucose metabolism and the impairment of the liver function, which affects the blood glucose levels, which causes hypoglycemia [8]. In T2DM patients, increased insulin resistance in key metabolic tissues, such as skeletal muscle, liver and adipose tissue, is coupled with the reduced insulin secretion caused by impaired β-cell function in the pancreas [9]. The impaired response to insulin and β-cell failure in the setting of alcohol-related insulin resistance, therefore, is critical in defining the risk and development of T2DM.

In this article, we review recent studies on the association

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between alcohol consumption and the incidence of diabetes and suggested underlying mechanisms that is focused on insulin resistance. Furthermore, this review describes the appetite regulating peptides, particularly ghrelin and leptin, along with the brain-derived neurotrophic factor (BDNF) that have been proposed as the basis for promising new therapies for diabetes.

ALCOHOL CONSUMPTION AND GLUCOSE METABOLISM

There is now quite some evidence that chronic heavy consumption of alcohol has deleterious effect on metabolic control and may even be associated with impaired insulin resistance. The pancreatic islet β-cells normally increase the insulin release sufficiently to overcome the reduced efficiency of insulin action. Thereby, maintaining normal glucose tolerance. However, chronic heavy alcohol use leads to impaired glucose tolerance, which is a combination of impaired secretion of insulin and a reduced insulin sensitivity or resistance. Glucose intolerance is the transition phase between normal glucose tolerance and diabetes, also referred to as prediabetes.

Plausible mechanisms mediating the association, between alcohol intake and glucose intolerance, have been hypothesized that disruption glucose homeostasis that may provide a specific mechanism by which, a chronic heavy ethanol consumption increases the incidence of T2DM. Meanwhile, compared to researches on the relationship between alcohol consumption and diabetic risk, among non-diabetic population, effects of alcohol on glycemic control in patients with T2DM have been studied at a much lower frequency. In alcoholism patients, diabetes has relevance to reduced insulin resistance, which is associated with chronic pancreatitis [10] or insulin secretion that is associated with alcohol-induced liver changes [11]. In general, when a shortage of glucose is impending, glucose will be secreted from glycogen stores in the liver, but glycogenolysis is also impaired by alcohol in which normal blood glucose levels cannot be maintained by the depletion of stores and hypoglycemia, which consequently may occur. Besides, continued alcohol metabolism causes diminished gluconeogenesis. Both the depletion of glycogen and diminished gluconeogenesis lead to lower blood glucose levels, as well as insulin secretion that is also reduced as the level of blood glucose falls.

Several findings concerning the involvement of chronic, heavy alcohol consumption in glucose metabolism is negative-

ly correlated with that of insulin concentrations, in addition to the fasting insulin levels. It has been reported that chronic high doses of alcohol alone have been exhibited to be efficient in producing reversible insulin resistance [12]. High concentrations of ethanol may lead to reduced insulin binding [13] and inhibition of intracellular signalling related to that of insulin [14]. Moreover, alcohol dependence was one of the concomitant factors in subjects with impaired glucose tolerance that are diagnosed with performing standard 75 g oral glucose tolerance test. This suggests that alcohol might impair fasting and postprandial glycemic controls and thus, alcohol consumption may be a risk factor for T2DM [15]. Extensive studies using animal models of chronic alcohol intake have provided insight into the possible mechanisms, which contributes to the development of diabetes. Previously, our study demonstrated that chronic heavy drinking aggravates T2DM. In this study, diabetic rats with chronic alcohol consumption showed lower fasting plasma glucose level, but significantly higher postprandial plasma glucose level that was difficult to return to baseline levels than the non-drinking diabetic rats. On the other hand, this effect of ethanol on glucose levels was not observed in the non-diabetic rats, which indicate that the diabetic state appears to be more susceptible to heavy alcohol ingestion than those in the non-diabetic state [16]. However, more attention needs to be paid to impact of chronic alcohol consumption on the glucose metabolism and insulin resistance that have already been described in patients with T2DM.

As noted above, the studies on glucose tolerance and insulin resistance in alcoholism focused on the impact of chronic heavy use of alcohol on the development of T2DM. Accordingly, deterioration in glucose homeostasis and insulin secretion in alcohol dependence may not only represent a consequence of T2DM, but also plays an important role in its cause, as well as its treatment.

PATHOPHYSIOLOGY OF DM

DM is a syndrome of disordered metabolism with abnormally high blood glucose levels, as a result of abnormal insulin secretion and/or signaling (hyperglycemia) [17]. Hypoglycemia shows abnormally low levels of glucose in the blood, which interfere with the function of organ system. The two most common forms of DM are type 1 (T1DM) and type 2 diabetes, with T1DM accounting for approximately 10% of all cases in Caucasians [18].

T1DM (insulin-dependent diabetes) results due to autoimmune progressive destruction of insulin-secreting β-cells of the pancreas by CD4^{+} and CD8^{+} T cells and macrophage infiltrating the islets [19]. The hormone insulin, secreted by the pancreas, involved in regulating body's blood glucose levels and other metabolic function. Most importantly, blood glucose is taken up into the muscle and fat tissues, by insulin, and existing glucose is converted into a storage form (i.e., glycogen), thereby lowering the blood glucose levels (e.g., after a meal). As a result of the immune system attack, the pancreas does not produce sufficient insulin. It usually occurs in childhood or adolescence, but can develop at any age.

In contrast, T2DM (non-insulin dependent diabetes) continue to produce insulin in the early phase of the disease; however, the body resists insulin's effect. Initially, resistance can be overcome by increasing insulin production. Eventually, the body can no longer produce enough insulin. A deficit in insulin secretion, coupled with the state of insulin resistance, leads to T2DM [20]. In most patients, the disease develops over age 40. Therefore, T1DM is characterized by a complete lack of insulin production, whereas, T2DM is characterized by a reduction of insulin production plus resistance [21]. Unlike T1DM, where insulin therapy can provide effective relief, T2DM requires treatment of insulin resistance, in addition to insulin secretion defects.

Hypoglycemia is defined as a state in which there are neuroglycopenic symptoms concurrent with a low blood glucose level. The definition of "low blood glucose" can differ significantly across the major medical associations. Although in general, T2DM shows a less hypoglycemia risk, when compared to that of T1DM, the frequency of hypoglycemia increases with increased diabetes and insulin treatment duration in T2DM [22]. In patients with either T1DM or T2DM, the root cause of factual hypoglycemia is always hyperinsulinemia. However, the etiology of hyperinsulinemia varies depending on the type of treatment strategy. For T1DM, hypoglycemia is always due to excessive insulin dosage. In T2DM, it results from the use of insulin or sulfonureas. The combination of a GLP-1 agent and a sulfonurea is a potent mixture and may cause lower than normal blood glucose levels (i.e., hypoglycemia).

ALCOHOL CONSUMPTION AND RISK OF T2DM

There are several studies conducted to determine if chronic use

of alcohol could be susceptible to a defective glucose tolerance, decreased insulin sensitivity, as well as an increased insulin resistance that implied elevated risk of developing T2DM. T2DM is characterized by a defect in insulin-mediated glucose uptake in the muscle, an impaired insulin secretion by pancreatic β-cells, a disruption of secretary function of adipocytes, and dysfunction of insulin action in the liver, which affects the whole body glucose homeostasis [23]. Impaired insulin signalling, combined with the eventual exhaustion of β-cell insulin production, causes T2DM. The development of both insulin resistance and impaired glucose tolerance, conditions that precede the onset of T2DM, are closely linked with alcoholism.

In T2DM, insulin sensitivity is reduced, while insulin secretion may be increased, resulting in hyperinsulinemia, especially in the early phase of the disease, or decreased, in comparison to the healthy subjects, with normal glucose tolerance [24]. The priming effect of alcohol-enhanced insulin secretion in pancreatic β-cells might be caused by an early defence mechanism, which is used to compensate for alcohol-inhibited basal insulin secretion. In contrast, a limited number of studies have reported deleterious effects of alcohol on β-cells, in which alcohol inhibited the insulin secretion [25]. As a result of β-cell dysfunction and inadequate insulin release, postprandial and subsequently fasting glucose levels increased, due to incomplete suppression of hepatic glucose production and decreased efficiency of liver and muscle glucose uptake. The extremely elevated blood glucose levels, with frequently observed diabetes, might contribute to further disease progression through the glucotoxic effects on the β-cell and harmful effects on insulin sensitivity, both of which can be ameliorated by therapeutically lowering the glucose level [26].

In addition, T2DM patients are typified by a decreased fat oxidative capacity and elevated levels of circulating free fatty acid [27]. The letter is known to cause insulin resistance by reducing stimulated glucose uptake, which most likely accumulated in the lipid inside the muscle cell [28]. A reduced fat oxidative capacity and metabolic inflexibility are important components of muscle insulin resistance [29]. Heavy alcohol consumption increases ROS production and may be a mechanism of pancreatic β-cells dysfunction in T2DM. The reason is that ROS production is one of the earliest events in glucose intolerance, through mitochondrial dysfunction. Further, β-cells are very sensitive to oxidative stress [30]. Previous studies of alcohol dependence have shown that alcohol elevated the level of β-cell apoptosis and increased insulin resistance in the liver and

skeletal muscle, which is among the earliest detectable alterations in humans with T2DM [20]. These studies demonstrated the diabetes-related lipid abnormalities, by insulin sensitivity, mediated oxidative stress and the altered metabolism has been shown to have a deleterious effects after heavy drinking, an effect mediated by insulin.

A POSSIBLE PATHOPHYSIOLOGICAL MECHANISM

Appetite regulating peptides, particularly ghrelin and leptin

One mechanism through which chronic use of alcohol might affect numerous processes that are aligned with neuroendocrinology of T2DM is through the alteration of appetite regulating peptides, particularly, ghrelin and leptin. It has been consistently found that neurobiological profiles of alcohol dependence are linked to the effects of T2DM, which are affected by the altered levels of ghrelin and leptin, which regulate food seeking behavior that have similar mechanism of controlling of alcohol craving behavior [31].

Ghrelin is the most potent endogenous orexigenic peptide of gastric origin that plays a proliferative or protective role on β-cells [32] and stimulates insulin secretion, which primarily occurs in the response to that of the increased circulation of glucose levels, whereas insulin reduced the plasma ghrelin level in normal control and T2DM patients [33]. Moreover, ghrelin may decline endogenous glucose production, through suppression of insulin secretory capacity [34], while reinforcing insulin action on the glucose disposal [35]. Leptin is an adipocyte-derived anorexic peptide that play a crucial role in regulating the metabolism of glucose overall and particularly glucose metabolism that suppresses the production of ghrelin via increase in insulin secretion and glucose utilization, along with the leptin exerts that elevates the ability in the development of diabetogenic imbalance, such as development of pancreatic β-cell dysfunction, insulin resistance, obesity, impairment of liver function in glucose metabolism by utilizing different mechanisms concurrently and sequentially [36]. In addition, therapeutic administration of insulin during 1 year resulted in increased the mean body weight and leptin concentrations, suggesting that insulin stimulated leptin secretion, which was believed to mediate the increase body weight [37]. Further, long period of leptin treatment led to decreased insulin-stimulated glucose utilization in skeletal muscle [38].

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. We recently reported that leptin potentially plays a role in the pathogenesis of T2DM affected by the insulin resistance in patients with alcohol dependence. Our results confirm the existence of significant correlation between leptin and the fasting insulin concentration, β-cell function and insulin resistance and also, alcohol consumption, might produce leptin resistance despite the study that will be needed to determine the mechanism of the relationship between alcohol intake and leptin resistance. Collectively, ghrelin and leptin appears to exert a wide functional interaction between these peptides, which may contribute significantly to the overall diabetogenic effects of chronic alcohol consumption, and are being further investigated.

BDNF

Given the data indicating decreased BDNF in alcoholism, there has been considerable interest in the possibility that chronic alcohol ingestion may impart its negative effects on T2DM, through its effects on BDNF. BDNF, a member of the neurotrophin family, mediated through a specific Trk family receptor tyrosine kinase B (Trk A, Trk B, and Trk C), is abundantly expressed in central and peripheral nervous system [39]. BDNF have received attention, regarding a possible role in regulating neuronal survival, differentiation, synaptic plasticity, cognitive function and memory.

The latter findings were low circulating levels of BDNF in individual with T2DM and the severity of insulin resistance by the homeostasis model assessment index, which is based on fasting glucose and insulin levels [40]. BDNF might also regulate glucose metabolism and reduces food intake and lowers blood glucose in the obese diabetic mice [41]. Further, some of the cognitive deficits observed in T2DM may be directly attributed to the impact of either high glucose levels or insulin glucose tolerance [42,43]. The decrement in memory function observed in subjects with impaired glucose regulation appears to be associated with hippocampal function and could be attributed to decreases in extracellular glucose levels in the hippocampus. Likewise, insulin, which plays a role in glucose transport in certain brain cell populations, through insulin-sensitive glucose transporters (GLUT4 and GLUT8) in various brain regions, including the hippocampus [44]. Interestingly, the effects of BDNF on T2DM and its association with cogni-

tive functions, such as learning and memory, have been investigated [45]. Both experimental and clinical research have shown that BDNF plays a critical role in insulin resistance, a pathogenic feature of T2DM, indicating that BDNF is a regulator of glucose metabolism by directly acting on the hypothalamus [41], and is thought to have a protective effect on the pancreatic islets [46]. However, the exact mechanism of BDNF linked to the pathophysiology of T2DM after alcohol ingestion has also not been completely understood as of yet.

Several investigators have addressed the impact of alcohol on the development of T2DM, affected by altered levels of BDNF, which modulate the activity of neurotransmitters, enhance cellular growth, and participate in neuronal plasticity [47]. Decreased in BDNF levels after chronic ethanol exposure supports the concept that ethanol-induced cell damage, which might be affected by BDNF, suggesting that BDNF involved in the process of neurogenesis is one of major targets of ethanol toxicity [48], as well. Recent research regarding alterations of BDNF in maintenance of alcohol dependence have showed that the acute administration of ethanol elevated the expression of BDNF mRNA in hippocampus neurons and that BDNF regulated the behavioral response to ethanol, but was decreased after continuous exposure [49]. There are possible underlying mechanisms of the homeostatic pathway, appearing that the potentiated release of dopamine and serotonin in striatal neurons by BDNF stimulation [50], the induction of receptors for activated protein kinase C (RACK1) expression and the dopamine D3 receptor [51], the alleged downstream component of the BDNF/RACK1 cascade, and successive changes in synaptic plasticity [52].

Much of our recent focus has been the role of BDNF, as an important regulator in the glucose metabolism and BDNF may be associated with an increased risk of T2DM in alcoholism. Our study reported that chronic heavy drinking-induced decreases the serum BDNF levels in a rat model of T2DM [16]. In this study, alcohol-treated rats presented significantly lower plasma BDNF level, than compared to those in the non-diabetic and non-alcohol-treated rats, which suggests that chronic heavy alcohol use and T2DM may create a synergic effect in the reduction of BDNF level. Alcohol-treated diabetic rats also presented significantly lower fasting plasma glucose level, but significantly higher postprandial plasma glucose, than those in the non-alcohol-treated diabetic rats. Findings of this study proposed that decreased BDNF may mediate between chronic alcohol consumption and aggravation of postprandial glyce-

mic control. Moreover, the decreased level of BDNF in the alcohol dependent patients in our study might be a reflection of the damaged BDNF/RACK1-related homeostatic pathway [53].

Consequently, BDNF have an important physiological function in alcohol metabolism, as well as roles in glucose metabolism and insulin resistance. Alcohol dependent subjects were found to have decreased plasma BDNF levels and impaired insulin resistance, which is a major pathogenic feature of T2DM. This might indicate that BDNF may be linked to the pathophysiology of T2DM after alcohol use.

Hippocampal long-term potentiation (LTP)

Hippocampal LTP, a functional marker of synaptic plasticity, is considered to be the basis in studying nervous and molecular mechanism of learning and memory [54]. Although there is accumulated evidence between T2DM and chronic heavy alcohol consumption, which is associated with the impairment of hippocampus-dependent cognitive functions, the combined effect on hippocampal LTP remains to be determined. In animal experimental studies that showed both, special learning and LTP expression in the hippocampus, were impaired in severely hyperglycemic rats as compared with those in the non-diabetic controls, however, spatial learning and hippocampal LTP were unaffected in moderately hypoglycemic rats, in morris water maze tests [55].

Interesting conceptual notions connecting the impact of chronic heavy use of alcohol and T2DM on hippocamal LTP processes also have been elaborated from alteration of endogenous BDNF. BDNF, acting through its TrkB receptor, plays a role in the synaptic plasticity and positively moderates processes, which leads to a stable LTP in hippocampus [56], as well as glucose metabolism in diabetes [41]. Recently, there has been a report that showed chronic heavy drinking decreases the serum BDNF levels in OLETF rats that provide a model for the pathophsiology of human T2DM [16], and decreased BDNF was also observed in rats displaying insulin resistance and LTP [57]. These studies suggest that better glycemic control improves cognition and that there is a cognitive benefit to improving BDNF level in T2DM. The fact that alcohol induced brain damages and cognitive dysfunction might precede other complications of alcohol, strongly suggests the need for research on their relationship. Alcohol-induced brain damages were commonly observed in otherwise, uncomplicated alcoholics [58]. Thus, brain is one of the most vulnerable organs from alcohol-induced toxicity.

In line with these, we recently reported that chronic heavy drinking impairs hippocampal long-term potentiation (LTP) in rat model of T2DM [59]. Considering that significantly lower fasting and postprandial glucose levels and relatively less weight gain of diabetic rats, with chronic heavy alcohol consumption compared to those of diabetic rats that never drink, such impairment of LTP, is a notable finding. Hippocampus has a key cerebral structure, which is related to learning and memory, in particular, long-term memory and is especially sensitive to the deleterious effects of glucocorticoid that was deregulated in patients with T2DM [60], as well as in the individuals with acute and chronic alcohol consumption [58]. Our finding implied that chronic alcohol consumption further impair hippocampal LTP, despite the non-aggravated glycemic control. Future clinical studies, using cognitive function test and neuroimaging modalities, will be needed. Thus, chronic heavy use of alcohol would be considered as a risk factor of potentiating cognitive decline in T2DM, which may increase the occurrence of pathopysiological changes associated with T2DM.

SUMMARY AND CONCLUSION

The findings discussed here presents that the role of chronic use of alcohol on diabetes might be high of importance for clinical research and practice. The finding that was shown may also help to explain previous contradictory findings, regarding the association between alcoholism and diabetes. Chronic heavy consumption deteriorates glucose tolerance and insulin resistance, and this may well be one of the mechanisms involved in the malignant effect of alcohol, with regard to development of diabetes. In addition, appetite-regulating peptides, particularly ghrelin and leptin, BDNF, and hippocampal LTP, which play important roles in the brain and insulin sensitivity, could become possible candidates for mediation that links T2DM and alcohol consumption. The novel mechanisms of these two appetite regulating peptides, BDNF and hippocampal LTP are widely involved in the neurobiology of alcohol dependence and T2DM. It deserves to be investigated more intensively in diabetogenic effects of chronic alcohol consumption. Therefore, understanding of the pathophysiological bases of these mechanisms should enhance better approaches to a potent therapeutic strategy for the treatment of both alcoholism and diabetes.

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