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Alcohol Toxicity in Diabetes and Its Complications: A Double Trouble?

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Critical Review

Alcohol Toxicity in Diabetes and Its Complications: A Double Trouble?

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Background: Eight percent of the U.S. population has been diagnosed with diabetes mellitus (DM), while another large percentage has gone undiagnosed. As the epidemiology of this disease constitutes a larger percentage of the American population, another factor presents a dangerous dilemma that can exacerbate the hazardous effects imposed by DM. Excessive alcohol consumption concerns the health of more than 50% of all adults. When this heavy-alcohol-drinking population overlaps with DM and its complications, the effects can be dangerous. In this review, we term it as "double trouble."

Methods: We provide evidence of alcohol-induced exacerbation of organ damage in diabetic conditions. In certain cases, we have explained how diabetes and alcohol induce similar pathological effects.

Results: Known exacerbated complications include those related to heart diseases, liver damage, kidney dysfunction, as well as retinal and neurological impairment. Often, pathophysiological damage concludes with end-stage disorders and even mortality. The metabolic, cell signaling, and pathophysiological changes associated with "double trouble" would lead to the identification of novel therapeutic targets.

Conclusions: This review summarizes the epidemiology, diagnosis, pathophysiology, metabolic, and cell signaling alterations and finally brushes upon issues and strategies to manage the "double trouble."

Key Words: Diabetes Mellitus, Alcohol Toxicity, Epidemiology, Pathophysiology, Cell Signaling, Aldehyde Dehydrogenase, Mitochondrial Dysfunction.

VERY RECENTLY, IT has been predicted that approximately half of the U.S. population will suffer from diabetes or prediabetes in 2020 if the modern lifestyle continues as present (United Health Group, 2010). The majority of the patients will have type 2 diabetes, which itself is associated with poor lifestyle choices, including an unhealthy diet constituting of high fat intake, high carbohydrate intake, as well as increased inactivity due to high electronics usage and limited exercise. In this review, we are going to address another layer of lifestyle-mediated hazardous effects on diabetic patients: alcohol toxicity. As heavy alcohol consumption is also associated with poor eating habits and reduced exercise, this may lead to diabetes or exacerbate diabetes-induced complications. Before addressing pathophysiological conditions associated with such complications, it is important to evaluate the clinical issues associated with alcoholic diabetics. Heavy drinkers, as well as moderate drinkers, consistently exhibit faulty obedience toward their self-treatment (Chew et al., 2005). This behavior includes the inability to follow insulin treatments, lack of regard for dietary choices, negligence toward medication regimens, and even inadequacy of visits to healthcare professionals (Chew et al., 2005; Cox et al., 1996; Howard et al., 2004; Karter et al., 2000).

At the metabolic level, oxidative stress is the major contributor of the pathogenesis of diabetic complications (Brownlee, 2005). In our laboratory, we study the toxic effects of the secondary products of oxidative stress known as reactive aldehydes, one being 4-hydroxy-2-nonenal (4HNE) (Mali and Palaniyandi, 2014; Mali et al., 2014). 4HNE is detoxified by aldehyde dehydrogenases (ALDH) (Vasiliou et al., 2000). In diabetic tissue, ALDH activity is decreased (Hamblin et al., 2007; Mali et al., 2014; Palaniyandi et al., 2010; Wang et al., 2011), which in turn jeopardizes the metabolism of reactive aldehydes and leads to the accumulation of more aldehydes. On the other hand, alcohol toxicity results in increased accumulation of acetaldehyde (Doser et al., 2009), a metabolite of ethanol (EtOH).

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Incidentally, acetaldehyde is metabolized by ALDH itself (Doser et al., 2009). Therefore, in diabetics with alcohol intoxication, the diabetes-induced decrease in ALDH2 activity might lead to further accumulation of acetaldehyde and other reactive aldehydes like 4HNE. Due to this, the risk of health deterioration is 2-fold, caused by both an increased prevalence of acetaldehyde, as well as the lowered activity of ALDH2. The former can induce symptoms such as palpitation, hypotension, and nausea. The latter, when in reduced levels in the diabetic heart, leads to mitochondrial dysfunction instigated by increased 4HNE adduct formation on mitochondrial complex proteins.

Collectively, this diabetes mellitus (DM)-induced and alcohol-induced insulin resistance and mitochondrial dysfunction are integral in developing complications such as cardiomyopathy. Additionally, it appears both diabetes and alcohol intoxication potentiate one another's adversity at the level of nutrition, metabolism, and pathophysiology. Recently, a study performed by Gardebjer and colleagues (2015) showed that regular alcohol drinking in pregnant rats resulted in lowered insulin sensitivity, as well as decreased glucose tolerance in afflicted fetuses. Furthermore, when these fetuses were given diets high in fat and cholesterol, the diabetes-related symptoms were compounded (Gardebjer et al., 2015). Often undermined by healthcare professionals, alcohol toxicity is a major component in inducing and exacerbating DM-related symptoms. This review will focus on the epidemiology, pathophysiology, metabolic signaling, and management strategies of the deleterious effects of heavy alcohol drinking in diabetes.

EPIDEMIOLOGY OF DIABETICS WITH ALCOHOL-DRINKING ISSUES

Diabetes and Alcohol-Drinking Issues in the General Public

In 2014, a staggering 29.1 million people were found to suffer from DM in the United States (CDC, 2014). Exacerbating this epidemic, 27.8% or 8.1 million people that had DM actually went *undiagnosed* (CDC, 2014). The total afflicted DM population in the United States primarily is encased within the "adult" population, as 28.9 million people who are 20 years or older suffer from the epidemic (99.3% of all diabetics) (CDC, 2014). Furthermore, after accounting for the entire adult population, it can be determined that 12.3% of all people aged 20 or older have DM (CDC, 2014). By 2050, however, it is predicted that 33% of the U.S. population will have DM (CDC, 2010). Around 87% of adults (aged 18 or older) in 2013 admitted to drinking alcohol at least once during their life (NIH-NIAAA, 2013). Furthermore, around 56% of this same adult population admitted to drinking in the previous month (NIH-NIAAA, 2013). With these 2 large separate populations that drink alcohol and suffer from DM, many overlaps can be common. Unfortunately, in this specific population of people that are both diabetic and alcohol drinking, many health-related issues can arise.

While moderate drinking has been proven to show a positive effect on DM and its associated complications (Baliunas et al., 2009; Carlsson et al., 2003; Tanasescu et al., 2001; Wei et al., 2000), more strenuous drinking has been associated with pathophysiology (Baliunas et al., 2009; Beulens et al., 2008; Blomster et al., 2014; Carlsson et al., 2003; Pitsavos et al., 2005; Tanasescu et al., 2001; Wei et al., 2000). This pattern of abusive drinking is not uncommon after all, as 24.6% of adults admitted to binge drink in the preceding month in the United States (NIH-NIAAA, 2013). Furthermore, chronic alcohol addiction is also a grave problem. Around 6.6% of all alcohol drinkers in the United States, equating to about 17.3 million people, are alcohol abusers who have extreme drinking habits (SAMHSA, 2014). If the present scenario continues, the risk for deleterious effects is exacerbated as a result of this double trouble (alcohol and DM) (Fig. 1).

Heightened Risk of Diabetes Caused by Excessive Alcohol Intake

Differentiating Type 1 and Type 2 DM. Type 1 DM is insulin-dependent DM (insulin deficiency). It is usually diagnosed in young people in their childhood or adolescence. It is triggered by the autoimmune destruction of the insulin-producing beta cells of the islets of Langerhans in the pancreas. Factors such as contact with viruses, dietary quality of early lifestyle, and vitamin D deficiency can cause the disease; however, genetics is one of the main culprits (MacNaught and Holt, 2015). Often, type 1 DM leads to impaired glucose handling due to lack of insulin, and subsequently hyperglycemia.

Type 2 DM is noninsulin-dependent DM (insulin resistance). It is characterized as a disease mostly originating in the adult period of a person's life, as one's lifestyle slowly reduces the sensitivity of the insulin, causing hyperglycemia. In many cases, it may be accompanied with hypertension, increased low-density lipoprotein (LDL), lowered high-density lipoprotein (HDL), hyperlipidemia, and obesity, which is collectively known as metabolic syndrome (Huang, 2009).

Among the diabetics, the type 2 DM patients are usually above the legal age of alcohol drinking, unlike most juvenile type 1 DM patients. Therefore, in many cases, this prevents alcohol-induced complications from arising in type 1 DM patients. Almost 90 to 95% of diabetics have type 2 DM, leaving behind only 5 to 10% of type 1 DM patients (American Diabetes Association, 2009). Nevertheless, even among type 1 DM patients, limiting alcohol-induced exacerbation of diabetes and associated complications would improve quality of life. Therefore, in this review, we will provide evidence available from both type 1 and type 2 diabetic studies, presumably more related to type 2 DM.

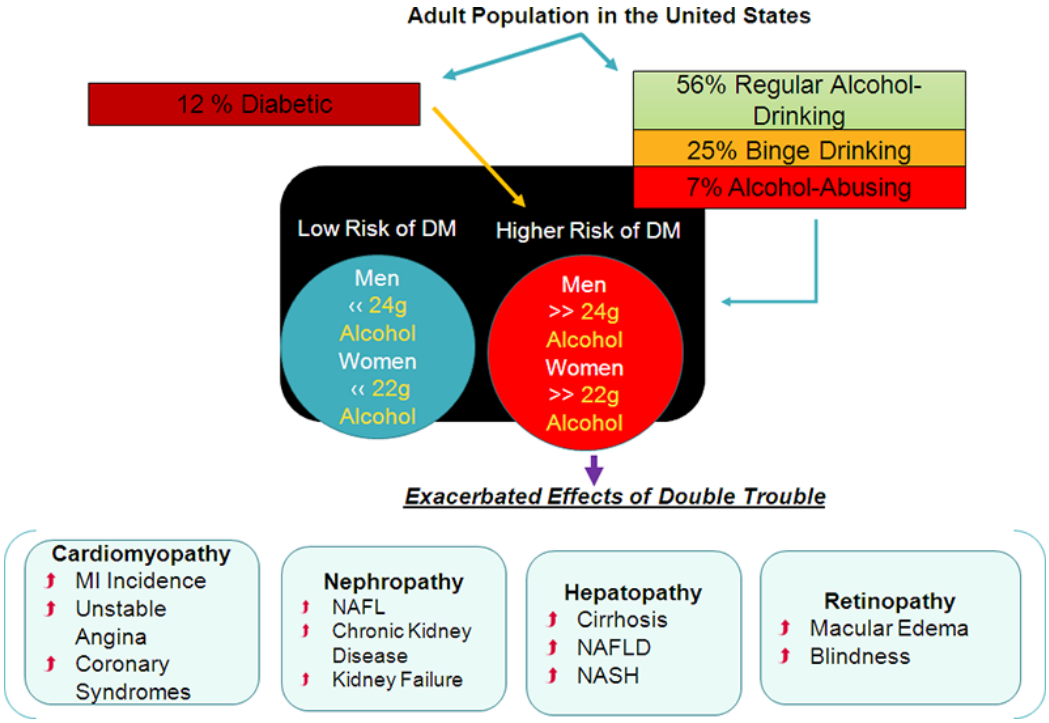

Fig. 1. Epidemiology of "double trouble." The extent of health risk for diabetics upon alcohol consumption in U.S. adult populations is shown.

Alcohol's Collective Effects on DM. Numerous studies have pointed out the protective effect of moderate alcohol intake in reducing the prospect of type 2 DM (Baliunas et al., 2009; Carlsson et al., 2003; Wei et al., 2000). Specifically, a meta-analysis taking into account past studies suggested that a maximum daily intake of 22 g of alcohol in men and 24 g of alcohol in women will abate the risk of type 2 DM (Baliunas et al., 2009). If moderate amounts are consumed, there could be a 30 to 40% decrease in the risk for DM both in women and in men (Carlsson et al., 2003). This reduction can be clearly seen in the U-shaped graph comparing alcohol intake and hazard of DM that many analyses have yielded (Baliunas et al., 2009). Despite this positive outlook on alcohol consumption on DM, a very strong negative attribution still exists. When women ingested more than 50 g of alcohol and men around 60 g of alcohol, the protective effect of alcohol vanished, and instead, an increased risk for DM was apparent (Baliunas et al., 2009). These amounts correlate to about 2 drinks every day (Baliunas et al., 2009). Furthermore, Kao and colleagues (2001) quantified this risk of DM due to excessive alcohol intake. It was determined that men who consumed more than 21 drinks a week had 50% increase in risk than similar men who consumed no more than 1 drink a week (Kao et al., 2001). Other studies point out a similar adverse affect. Wei and colleagues (2000) concluded that when comparing moderate and excessive alcohol drinkers, a 2-fold escalation in the risk of DM was found in the excessive drinking group. As per these studies, the prospect of *single trouble* (alcohol) leading to *double trouble* could be alarming.

We are more interested in the effects of alcohol on diabetes-induced complications than diabetes itself. In particular, we are interested in diabetic cardiac complications as more than 60% of type 2 diabetics and more than 40% of type 1 diabetics die of heart diseases (de Ferranti et al., 2014; Laakso, 2010). Therefore, in our review, we will highlight the effects of alcohol on diabetic complications with a heavier emphasis on cardiac complications.

Diabetic Complications Associated with Alcohol Intake

Diabetic Heart Diseases. Diabetics have a 1.7-, 1.8-, and 1.5-fold increase in the risk for cardiomyopathy-induced mortality, heart attacks, and strokes, respectively, compared to nondiabetics (CDC, 2014). While moderate drinking has been shown to lower cardiovascular complications in people with DM, excessive drinking has also been shown to reverse the positive effect (Blomster et al., 2014). A J-shaped graph is obtained when comparing the amount of EtOH consumed against the risk of cardiovascular disease (Pitsavos et al., 2005). While initially, there is a beneficial effect, after a threshold of 12 g of EtOH consumed, the risk of cardiovascular disease increases by 47% (Pitsavos et al., 2005). The risk for acute events is also heightened, as men who consumed more than 21 drinks a week and women who consumed more than 14 drinks a week (heavy drinkers) experienced an increased risk for cardiovascular events, microvascular events, and even death (Blomster et al., 2014).

In diabetics who drank 12 to 24 g of alcohol daily, the risk of total acute coronary syndromes increased more than

5 fold compared to those who drank a limited amount (<12 g daily) (Pitsavos et al., 2005). When this limited group was compared to extreme drinkers (more than 24 g daily), the risk escalated by more than 10-fold (Pitsavos et al., 2005). Furthermore, when examining myocardial infarction rates, the risk increased by almost 8-fold in heavy drinkers (more than 24 g daily) compared to a limited alcohol consuming group (<12 g daily) (Pitsavos et al., 2005). In terms of unstable angina, the risk grew by more than 13-fold in heavy drinkers (more than 24 g daily) compared to limited drinkers (<12 g daily) (Pitsavos et al., 2005). These dramatic increases in cardiovascular risks serve to prove the reoccurring J-shaped relationship that exists between alcohol consumption and acute cardiac events.

Taken together, the potentiation of cardiac diseases in diabetes with alcohol toxicity will be multifold.

Diabetic Nephropathy. DM-induced neph-ropathy is a major reason for kidney failure (CDC, 2014). In 2011, around 44% of all cases involving kidney deterioration were related to DM in the United States (CDC, 2014). In the same year, almost 230,000 diabetics underwent dialysis or even transplantation to treat DM-induced kidney failure (CDC, 2014).

In patients with DM or obesity, the risk of nonalcoholic fatty liver (NAFL) escalates by 60 to 90% (Targher et al., 2012). Additionally, with the addition of new studies, it is now suggested that those with NAFL, problematically, are now in greater danger of developing chronic kidney disease (Targher et al., 2012). Alcohol intake, when kept to moderation, has been shown to lower the risk of renal cell carcinoma; however, excessive amounts have been linked to numerous complications, including postinfectious glomerulonephritis, immunoglobulin A nephropathy, kidney graft failure, acute kidney injury, renal papillary necrosis, as well as the deadly end-stage renal disease (ESRD) (Perneger et al., 1999; Schaeffner and Ritz, 2012). In a recent study, Perneger and colleagues (1999) found that the consumption of more than 2 drinks daily can increase the risk of ESRD by 4-fold. Furthermore, it was also found that limiting this habit of 2 drinks daily can minimize the total diagnoses of ESRD by 9% in the diabetic population (Perneger et al., 1999). Patients who simultaneously suffer from DM and consume excessive alcohol can experience disastrous effects on the kidneys, both directly, and indirectly.

Diabetic Hepatopathy. Liver disease is the fourth leading cause of death in type 2 diabetic patients (de Marco et al., 1999). For instance, liver cirrhosis accounted for 5 to 12% of diabetes-related deaths (de Marco et al., 1999). Diabetic liver diseases comprise of abnormal liver enzymes, nonalcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure (Diehl and Choi, 2008; El-Serag et al., 2004). Patients with diabetes have a high prevalence of liver disease, and on the other hand, patients with liver disease or alcoholic liver disease have a high prevalence of diabetes (Tolman et al., 2007). NAFLD is found in many obese patients with a wide spectrum of diseases associated with metabolic syndrome, including type 2 DM (Diehl and Choi, 2008). In particular, in patients with type 2 DM, NAFLD can result in nonalcoholic steatohepatitis (NASH), which is shown to greatly increase the risk of complex cirrhosis and even death (Chandrasekaran et al., 2012; Diehl and Choi, 2008). Diehl and Choi (2008) reported that NASH can increase the occurrence of cirrhosis in obese people (with type 2 DM) by 75 times. This is especially concerning, as 87% of diabetics with NAFLD also had NASH (Diehl and Choi, 2008).

Alcohol-related cirrhosis constitutes a major proportion of all cirrhosis-related mortalities in the United States (NIH-NIAAA, 2013). Around 48.0% of all cirrhosis-related deaths were caused by excessive alcohol consumption (NIH-NIAAA, 2013). In the population of people aged 25 to 34, a staggering 72.7% of all cirrhosis diagnoses were related to alcohol (NIH-NIAAA, 2013). When type 2 diabetics consume alcohol, an altogether synergized risk of cirrhosis is prevalent. As type 2 DM progresses, NASH and alcohol-induced cirrhosis can become a formidable toxic combination.

Diabetic Neuropathy. Frequently, diabetic neuropathy results in nerve pain in the legs (Fowler, 2008). In certain extreme cases, numbness associated with the nerve damage can lead to negligence in noticing scrapes or ulcers (Fowler, 2008). These problems can lead to serious infections, which may then have to be treated with amputations (Fowler, 2008). In 2010, DM alone caused around 60% of all pathological, nonacute lower body amputations (CDC, 2014).

Several studies have shown that consuming alcohol while suffering from DM can lead to an enhanced risk of neuropathy (Emanuele et al., 1998). McCulloch and colleagues (1980) reported that diabetic men who had 3 to 4 drinks daily had a higher risk of developing diabetic neuropathy and its associated nerve pain than diabetics who had fewer drinks. Later, Mitchell and Vinik (1987) accentuated these results by proving that diabetics who ingested at least 8 drinks weekly more rapidly acquired the symptoms of neuropathy than diabetics who drank a lesser amount of alcohol.

Diabetic Retinopathy. Another common diabetic complication, retinopathy is found in around 25.8% of all diabetics (CDC, 2014). With damaged blood vessels in the retinal area, diabetic retinopathy can lead to vision defects (CDC, 2014). In more severe cases, such as in the rare 4.4% of diabetics, progressive diabetic retinopathy can bring upon advanced macular edema and even complete loss of vision (CDC, 2014).

In a clinical investigation, it was found that diabetics who did not suffer from retinopathy initially were found to possess a greater chance in acquiring the disease if they drank at least 10 pints of beer weekly (Young et al., 1984). Nondrinking diabetics exhibited an opposite result, as the risk for

retinopathy was much lower (Young et al., 1984). Furthermore, these findings were accentuated by Kohner and colleagues (1998) through the United Kingdom Prospective Diabetes Study, which revealed that alcohol-drinking diabetic men had more cases of diabetic retinopathy than alcohol abstaining diabetics.

ISSUES IN DIAGNOSING AND TREATING DIABETICS WITH HEAVY-ALCOHOL-DRINKING PROBLEMS

Drinking issues are usually not diagnosed accurately. Most of the time, the amount of alcohol consumption is self-reported and most drinking habits are sporadic. Therefore, it is difficult to diagnose and treat diabetics who are heavy drinkers.

Acknowledging the Patient's Chronic Drinking Issues

In a recent case study conducted by Alromaihi and colleagues (2012), an aged female type 2 diabetic (named S.E.), who was undergoing therapy using metformin and glipizide, was admitted into a hospital for a routine health checkup. As an obese female with near hypertension, she had a hazardous A1c of 11% (Alromaihi et al., 2012). Also, with increased cholesterol, heightened triglycerides, low HDL, and high LDL, many symptoms of metabolic syndrome were apparent (Alromaihi et al., 2012). When asked about alcohol intake, she reported about 360 g of alcohol intake daily through mainly spirits (Alromaihi et al., 2012). Despite encouragement from her caretakers, she refused to reduce intake of alcohol or even seek help for her excessive drinking habits (Alromaihi et al., 2012).

The prevalence of such patients, especially in the United States, is unexpectedly high. Throughout their past, diabetic alcoholics may have consumed large amounts of alcohol and will continue to do so, even if strongly advised to reconsider. As patients' unhealthy choices continue to exacerbate DM, it is not uncommon to see a near-fatal event occur. In this specific case study, the excessive alcohol led to esophageal varices, and subsequently gastrointestinal bleeding, which altogether led S.E. to completely stop alcohol consumption (Alromaihi et al., 2012). When events like this occur, it is the healthcare provider's job to encourage and motivate patients to acquire habits and changes of thought that will accommodate their own medical situations, otherwise, repeated experiences can turn deadly.

The Risk of Hypoglycemia in the Diabetic Alcoholics

Excessive alcohol consumption in the diabetic can pose serious problems. A general study showed that around 17% of all the cases of hypoglycemic events in diabetics were caused by alcohol consumption alone (Engler et al., 2013; Pedersen-Bjergaard et al., 2005).

In the case of S.E., the primary concern of the healthcare provider is to dramatically lower the A1c to a safe level using insulin therapy, while making sure that the risk of hypoglycemia is low. Having unsteady treatments of insulin combined with chaotic scheduling can only exacerbate the patient's condition and cause hypoglycemia.

Heavy alcohol drinking may deteriorate the levels of plasma glucose. This in turn can cause overdischarge of insulin, which may dangerously lower glucose in the blood (resulting in hypoglycemia) (Alromaihi et al., 2012). In other cases, hepatic gluconeogenesis may become diminished, which can also lead to hypoglycemia (Alromaihi et al., 2012). In many cases, while the risk of hypoglycemia is certainly alarming, the rise in A1c levels over time represents a greater danger.

PATHOPHYSIOLOGY OF DOUBLE TROUBLE IN END-ORGAN DAMAGE

As of now, there are no clinical or preclinical research studies on end-organ damage in alcohol consumption in the diabetic condition. Hence, we strategized to present evidence either from diabetic complications or alcohol abuse-induced organ damage.

Diabetic Cardiomyopathy

During DM, the heart undergoes various, yet substantial structural and functional changes. A clear structural change can be apparent in left ventricular hypertrophy (LVH), derived through severe inflammation shown by the increased prevalence of C-reactive protein (CRP) and fibrinogen (Hayat et al., 2004). LVH involves the expanding of the left ventricle due to the increased stress of the heart to fulfill the body's requirements. As the size of the ventricle's wall abnormally increases, contractions become more difficult to execute, and the heart loses its circulatory ability. LVH is finally diagnosed when the LV mass exceeds 125 g/cm^3 in men and 110 g/cm^3 in women (Hayat et al., 2004).

Systolic and diastolic functional deterioration is also common in patients with DM. Systolic deterioration can be seen with a minimized LV ejection fraction, and diastolic decline is evidenced by lowered rates of LV relaxation and diastolic filling (Hayat et al., 2004). Additionally, aldosterone-associated fibrosis may be caused by excessive generation of collagen, as well as a proliferated fibroblast population (Brilla and Weber, 1992; McEwan et al., 1998; Young et al., 1995). This fibrosis may occur in the perivascular and interstitial areas of heart tissue (Factor et al., 1980). Furthermore, due to dyslipidemia as well as hyperglycemia that occur simultaneously with type 2 DM, changes in the endothelium can be prevalent (Hayat et al., 2004). Type 2 DM has been shown to cause degradation of the capillary endothelium, disjoint the intercellular junctions, and modify production of key glycoproteins attached to endothelial cells (Hayat et al., 2004; Tooke, 1995). Also, it is well documented that patients with endothelial alterations have an increased risk of developing atherosclerosis as well as congestive heart failure after heart

attacks due to the impaired ancillary circulation in the heart (Hayat et al., 2004).

Alcohol-Exacerbated Effects

A main component of further exacerbation of cardiac function by alcohol can be seen through changes in cardiomyocyte function. Particularly, there are 2 pathophysiological transformations seen (Molina et al., 2014). A key alteration is in mitochondrial function, seen when alcohol inhibits glutathione, which allows for reduced function of antioxidants, and thus increased oxidative stress affliction toward cardiomyocytes, and higher rates of apoptotic death (Vendemiale et al., 2001). Next, aberrations in calcium signaling lead to an overexpression of the L-type calcium channel, which can stimulate calcium accumulation, and thus exacerbate apoptosis and dysfunction in cardiomyocytes (Guppy et al., 1995).

Furthermore, the progression of cardiac fibrosis associated with the intake of alcohol can lead to a series of pathophysiological changes. Cardiac fibrosis caused by increased oxidative stress through the overaccumulation of collagen in the cardiac tissue leads to impaired ventricular filling, diastolic dysfunction, lowered LV ejection fraction, as well as LV dilation, all structural alterations to the heart (Molina et al., 2014; Piano, 2002). Interestingly, these same complications that accompany alcohol-induced cardiac fibrosis are also prevalent in DM-associated patients, further exacerbating the remodeling of cardiac architecture and functional disarray.

Diabetic Nephropathy

Due to DM-induced relaxation of glomerular arterioles, an overall escalated rate of filtration is seen (Zelmanovitz et al., 2009). This can account toward an increased rate of renal perfusion, especially dangerous as albumin can be released to the glomerulus from the capillaries (Zelmanovitz et al., 2009). In turn, the glomerular basement membrane is enlarged and there is severe affliction toward podocytes and therefore defective glomerular function (Zelmanovitz et al., 2009).

Additionally, in DM, a correlative high amount of CRP, tumor necrosis factor (TNF)-α, as well as interleukins 1, 6, and 28, can be recorded (Zelmanovitz et al., 2009). All of these can be indicative of markers for severe inflammation and are related to albuminuria as well as are key mechanisms for development of ESRD (Zelmanovitz et al., 2009).

Alcohol-Exacerbated Effects

In excessive alcohol consumption, the glomerular basement membrane becomes strikingly enlarged due to excessive cell proliferation (Epstein, 1997); especially in kidney tubules, damaged cells become expanded and structurally transformed (Epstein, 1997). Thus, kidney swelling is prevalent in heavy drinkers, resulting in incapacitation of key nephron function (Epstein, 1997). This alcoholic-induced nephromegaly further exacerbates similar structural alterations initiated by DM and therefore can result in severe podocyte damage, as well as impaired glomerular function (Epstein, 1997).

Diabetic Hepatopathy

The primary changes that occur in the liver in DM are accentuated by the progression of fatty liver disease. Throughout this process, 3 factors are crucial in determining the course: TNF-α, adiponectin, and fatty acids (Chaldakov et al., 2003; Klaus, 2004; Rajala and Scherer, 2003). Free fatty acids (FFA) are present in the liver and fatty tissue and often travel between the two (Diehl and Choi, 2008). Furthermore, they are especially important in the production of TNF-α and adiponectin (Kershaw and Flier, 2004). Both of these mentioned cytokines are important in regulating hepatocytes (which manage fat accumulation in the liver) (Diehl and Choi, 2008). Adiponectin allows for the reduction of lipids in the liver by lowering intake of fatty acids and increasing dispensing and oxidation of fatty acids (Diehl and Choi, 2008). It also increases the sensitiveness of insulin (Arner, 2003). However, TNF-α is an antagonist toward adiponectin, helping to create steatosis in hepatocytes and causing further desensitization of insulin (Chaldakov et al., 2003). Additionally, when TNF-α levels are superior to adiponectin's presence, this increases production of reactive oxygen species (ROS), enlists inflammatory conditions in the liver, as well as causes apoptosis of hepatocytes, which can cause steatohepatitis (Diehl and Choi, 2008; Pessayre et al., 2002). In further studies, these same comparative levels have been proven to cause NASH, a deadly and fatal liver disease (Hui et al., 2004).

Alcohol-Exacerbated Effects

By disrupting mitochondrial pathways, alcohol inhibits oxidation of FFA, which leads to their accumulation in the liver (Baraona and Lieber, 1979). Over time, lipotoxicity can be triggered due to abnormal levels of FFA and triglycerides and can lead to steatosis and apoptosis (Molina et al., 2014). Considering the fatty liver that already presents itself in DM, alcohol would further exacerbate this condition and in essence, can increase the risk of developing conditions such as steatosis. Furthermore, other pathophysiological changes induced by alcohol include promotion of inflammatory cells in the liver, overexpression of inflammation-inducing cytokines, creation of ROS, as well as oxidative stress from cellular damage in the liver (Gao and Bataller, 2011). All of these factors have been shown to increase the risk of steatohepatitis in heavy drinkers (Gao and Bataller, 2011). Unfortunately, in DM-associated patients, these inflammation-characterized conditions can be further exacerbated, leading to increased

risks for conditions such as steatohepatitis and cirrhosis, dangerous end-stage liver damage (Molina et al., 2014).

Hepatocyte damage is another mainstay of chronic alcohol usage. Acetaldehyde, a metabolite of alcohol metabolism, has been shown to mitigate functional processes in hepatocytes, increase oxidative stress, and exacerbate fat peroxidation (Setshedi et al., 2010). It may also target key proteins like collagen, which can lead to additional toxic adduct synthesis (Casini et al., 1991). In DM, this is especially hazardous, as hepatocytes are already afflicted by the inflammatory and ROS-induced conditions created by TNF-α and adiponectin (Diehl and Choi, 2008).

Diabetic Retinopathy

Diabetic retinopathy is mainly associated with the increased activity of aldose reductase in creating alterations in the polyol pathway, which changes glucose into glucose alcohol (Fowler, 2008). Due to hyperglycemia associated with DM, increased activity with the pathway results in sorbitol-exacerbated osmotic stress (Fowler, 2008). This key development can cause creation of microaneurysms, enlargement of inner layer membranes, and pericyte damage, all devastating to the health of the eye (Fowler, 2008).

Additionally, increased activity of vascular endothelial growth factor and growth factor beta (prevalent in DM) plays important roles in progressing retinopathy (Fong et al., 2004; Fowler, 2008). With these cases, retinopathy is reported as background retinopathy and/or proliferative retinopathy (Fowler, 2008). Background retinopathy entails retinal bleeding in the shape of small circles, formation of rough exudates, edema, and as mentioned previously, microaneurysms, whereas proliferative retinopathy includes vitreous hemorrhage caused by overproduction of blood vessels on the retina, as well as partial or complete blindness in the progressed pathological stage (Fowler, 2008).

Alcohol-Exacerbated Effects

A main complication of alcohol-induced eye disease is central serous retinopathy (CSR). It mainly involves the removal of the retinal pigment epithelium from the eye tissue, occurring through many unique methods such as bullous, multifocal, bilateral, and extrafoveal removal (Gkotsi et al., 2013). Supportively, recent studies such as the one by Haimovici and colleagues (1997) have shown a causative relationship between alcohol consumption and intensity of CSR. In other cases, alcohol has been known to exacerbate hemorrhage occurrences and exudate formation, especially troublesome as these are the very conditions that already exist in DM (Abe et al., 1995). Additionally, alcohol has been known to cause abnormal transudation of fluid, resulting in blockages in the capillaries and venous areas (Prunte and Flammer, 1996). This is also concerning, due to the proliferative and enlarging themes of retinopathy seen in DM. Furthermore, oxidative stress caused by alcoholism can cause the nitration of tyrosine in cellular proteins, which can deteriorate the effectiveness of the outer blood–retina barrier, increasing the risk of harmful substances advancing to the delicate retinal areas (Haussinger and Schliess, 2008; Murthy et al., 2001).

Diabetic Neuropathy

Neuropathy in patients with DM is usually associated with the intensity of hyperglycemia (Fowler, 2008). Nevertheless, any hyperglycemic state will allow for the 3 main mechanisms that induce neuropathy: slowed rheological function, oxidative stress, and polyol aggregation (Fowler, 2008). In the hyperglycemic state, blood flow through nerves is lowered and there is greater endothelial vascular pressure (Miranda-Massari et al., 2011; Tooke, 1996). Key compounds such as myoinositol are also lost, which adds to the rheological damage (Miranda-Massari et al., 2011). With oxidative stress, increased activity of protein kinase C alters key metabolic pathways, which can cause defective axoplasmic transport as well as vascular affliction (Inoguchi et al., 2003; Miranda-Massari et al., 2011).

Also, an increase in aldose reductase activation allows for aggregation of sorbitol (through the glucose to sorbitol pathway) and thus causes damaging glycosylation of key proteins needed in the peripheral nervous system (Miranda-Massari et al., 2011).

The most prevalent type of neuropathy is chronic sensor motor distal symmetric polyneuropathy, which essentially results in loss of sensation to touch, temperature, and vibration (Bansal et al., 2006; Fowler, 2008). This type of neuropathy is also associated with a needle-like pain that occurs in many patients (Bansal et al., 2006; Fowler, 2008). Another common type of neuropathy is DM-induced autonomic neuropathy (Bansal et al., 2006; Fowler, 2008). This entails many serious conditions such as gastroparesis, digestive problems, tachycardia, bladder failure, anhidrosis, silent ischemia, and erectile dysfunction (Bansal et al., 2006; Fowler, 2008). Autonomic neuropathy is also known for its burdensome amount of mortality (Fowler, 2008).

Alcohol-Exacerbated Effects

Alcohol-induced neuropathy is mainly caused by the weakening of axons and thinning of the myelin sheath covering nerve fibers. In any case, alcohol, other than altering transport of axons and agitating cytoskeletal structure, has been proven to increase oxidative stress, by diminishing antioxidant concentrations, creating new ROS, as well as promoting fat peroxidation (Montoliu et al., 1994). The created ROS products cause free radical damage to already-damaged nerves in DM, exacerbating the neuropathy (McDonough, 2003). Furthermore, alcohol can also induce neuropathy through its metabolite acetaldehyde (Chopra and Tiwari, 2012). Unlike EtOH, acetaldehyde directly represents a neurotoxic hazard, through its abilities to impair spinal cord function and disturb key neuronal organelles

(Goodlett and Horn, 2001). The pathological changes in multiple organ systems are summarized in Table 1.

CELL SIGNALING ABERRATIONS IN ALCOHOL INTOXICATION AND DIABETES

The major cell signaling changes associated with diabetes are those related to oxidative stress, mitochondrial dysfunction, glucose auto oxidation and advanced glycated end products (AGE), aberrant protein kinase C signaling, renin-angiotensin-aldosterone system (RAAS) activation, abnormal lipid/fatty acid metabolism, aldehydic stress, and impairment of ALDH2, as well as inflammation. There are a lot of reviews that detail key signaling changes in diabetic complications of multiple organs such as the heart (Brownlee, 2005; Reusch, 2003), liver (Garcia-Compean et al., 2009), kidney (Reidy et al., 2014), eye (Ciulla et al., 2003), and peripheral nervous system (Yagihashi et al., 2011). The cell signaling changes with long-term alcohol abuse or binge drinking result in detrimental consequences to the organs. Similar to DM-induced complications, many reviews that address cell signaling changes and mechanisms in the heart (Guzzo-Merello et al., 2014; Piano and Phillips, 2014), liver (Williams et al., 2014), and other organs (Jung et al., 2011) can be referred for individual organ damage with alcohol toxicity. Broadly, these changes are oxidative stress-induced abnormal signaling, mitochondrial dysfunction and impaired bioenergetics, calcium overload and abnormality, aldehydic (carbonyl) stress and ALDH2 inactivity, activation of RAAS, and cytokine signaling changes with inflammation. As our laboratory is interested in the aspects of oxidative stress-induced reactive aldehyde toxicity and ALDH2 impairment, we will discuss this topic and mitochondrial dysfunction in both alcohol toxicity and diabetic complications. We will also highlight key aspects of cell signaling changes in terms of cardiac pathology only.

Table 1. Pathophysiological Effects of Alcohol and Diabetes on Organs

Organ	Diabetes	Alcohol
Heart	Diastolic dysfunction LV hypertrophy Fibrosis Atherosclerosis Myocardial infarction	Contractile dysfunction LV dilation Fibrosis Myocardial infarction
Kidney	Impaired glomerular apparatus Microalbuminuria Macroalbuminuria End-stage renal disease	Nephromegaly Impaired fluid handling Electrolyte disturbances Hepato-renal disease
Liver	Fatty liver disease ROS-induced inflammation Steatosis NASH	Steatosis Steatohepatitis Cirrhosis NASH
Eyes	Microaneurysms Pericyte damage Rough exudate formation Edema Vitreous hemorrhage	Vitreous hemorrhage Rough exudate formation Impaired blood–retina barrier
Peripheral nervous system	Chronic sensor motor distal symmetric polyneuropathy Gastroparesis Tachycardia Bladder failure Anhidrosis Silent ischemia Erectile dysfunction	ROS-induced oxidative stress Impaired spinal cord function

LV, left ventricular; NASH, nonalcoholic steatohepatitis; ROS, reactive oxygen species.

ALDEHYDE STRESS AND ALDH2 IMPAIRMENT IN DIABETES AND ALCOHOL TOXICITY

Diabetes-induced hyperglycemia leads to ROS generation (Brownlee, 2005). Upon lipid peroxidation of polyunsaturated fatty acids in biological membranes, reactive aldehydes such as 4HNE are generated (Mali and Palaniyandi, 2014). These secondary products of oxidative stress can form adducts with proteins and DNA which can result in cellular dysfunction (Mali and Palaniyandi, 2014). Another source of reactive aldehydes (carbonyl stress) in diabetes is caused by glucose toxicity due to excessive cellular glucose (Jaganjac et al., 2013). This is manifested as glucose autoxidation, protein kinase C activation by production of diacyl glycerol, methylglyoxal formation and glycation, hexosamine metabolism, sorbitol formation, and changes in oxidative phosphorylation (Brownlee, 2005). Most importantly, the metabolic products of such anomalous glucose metabolism lead to generation of AGE and other glucose-derived carbonyl compounds which have long-lasting detrimental impacts on cellular function (Singh et al., 2014). For instance, 4HNE forms adducts on mitochondrial complex proteins (Lashin et al., 2006), proteasome subunits (Farout et al., 2006), and alters cellular functions (Dubinina and Dadali, 2010). When 4HNE was incubated with cardiomyocytes, it increased protein adducts and attenuated mitochondrial respiration (Hill et al., 2009). 4HNE and other aldehydes are detoxified by ALDH isozymes, glutathiones, and aldose reductase. ALDH2, a cardiac mitochondrial enzyme, levels and activity are reduced in the diabetic heart, accompanied by an increase in 4HNE protein adducts (Hamblin et al., 2007; Palaniyandi et al., 2010; Wang et al., 2011; Zhang et al., 2012). ALDH2 overexpression (Zhang et al., 2012) and activation of ALDH2 by Alda-1 (Palaniyandi et al., 2010), a pharmacological agonist of ALDH2, attenuated diabetic cardiac dysfunction and remodeling by reducing 4HNE adduct formation. In cultured cardiomyocytes, 4HNE was shown to reduce mitochondrial respiratory reserve capacity by forming protein adducts dose dependently (Hill et al., 2009). We have recently shown 4HNE or ALDH2 inhibition reduces mitochondrial respiration and reserve capacity in cultured cardiomyocytes (Mali et al., 2016). However, the overexpression of ALDH2 attenuated mitochondrial damage in streptozotocin-injected diabetic

hearts (Zhang et al., 2012). ALDH2 activation by Alda-1, an agonist of ALDH2 conferred cardio-protection against experimental diabetes by improving mitochondrial function with reduced 4HNE adduct formation (G. Pan, unpublished data).

Ren and Wold (2008) have summarized the EtOH- and acetaldehyde-induced cardiotoxicity and cardiac dysfunction in periodic reviews (Zhang and Ren, 2011; Zhang et al., 2004). Increased acetaldehyde can form adducts with proteins and damage cellular function (Nakamura et al., 2000; Setshedi et al., 2010; Worrall et al., 2000). Upon EtOH consumption, ALDH2 converts acetaldehyde into acetic acid and eliminates it from the body. Therefore, overexpression of ALDH2 reduces the pathology of alcoholic cardiomyopathy (Doser et al., 2009). Conversely, ALDH2*2, a mutant form of ALDH2 with low activity, increases the toxic effects of alcohol consumption (Zhang and Ren, 2011). It has noticeable negative effects in East Asians with this mutation (Nakamura et al., 2002). In clinical observations, ALDH2 mutation is associated with increased propensity to develop diabetic complications (Suzuki et al., 2004). In our ongoing studies, we found acute diabetes reduces mitochondrial respiration in ALDH2*2 mutant mice (Pan et al., 2015). The worst scenario is when diabetics increase alcohol consumption to toxic levels chronically. At this point, chronic hyperglycemia increases 4HNE adduct and decreases ALDH2 activity. Additionally, if diabetics drink alcohol excessively, this will lead to increased accumulation of acetaldehyde due to reduced ALDH2 activity.

There are no studies that have explored the consequences of excessive acetaldehyde and 4HNE-like reactive aldehydes with impaired ALDH2 activity. As ALDH activity is based on the availability of substrates (aldehydes) and cofactor (nicotinamide adenine dinucleotide), it will be very useful to carry out studies that investigate effects of different aldehydes on each other's metabolism and overall cellular function and metabolism.

ISSUES AND STRATEGIES TO COMBAT THE "DOUBLE TROUBLE"

In this section, we will provide our views on issues and then ideas to resolve them. First, the recognition of "double trouble" is very vital for management. It is crucial to investigate the change associated with the precedence of diabetes or alcohol intoxication on one another. Let us say if a patient is type 1 diabetic, the onset of diabetes may precede alcohol intoxication in the majority of cases. Because type 1 DM is a juvenile disease, it may be possible that by the time afflicted patients reach middle age, they may have already experienced a few decades of hyperglycemia. The onset of diabetic complications may start around this time, near a period of heavy drinking. On the other hand, if a patient is type 2 diabetic, drinking habits precede the onset of diabetes.

Another important issue is that heavy drinking is a subjective phenomenon; affected individuals perceive intoxication through emotional, psychological, and mood-oriented symptoms. Occasionally, it may be associated with the reactions their bodies exhibit such as headaches, vomiting, or palpitations. Unfortunately, individuals themselves or even diagnostic measures would miss important components that underlie changes in metabolism, cell signaling, and ultimately their pathogenesis. Therefore, the first important step is identifying and validating reliable biomarkers based on the progressive changes in metabolism, cell signaling, and pathophysiology pertaining to double trouble.

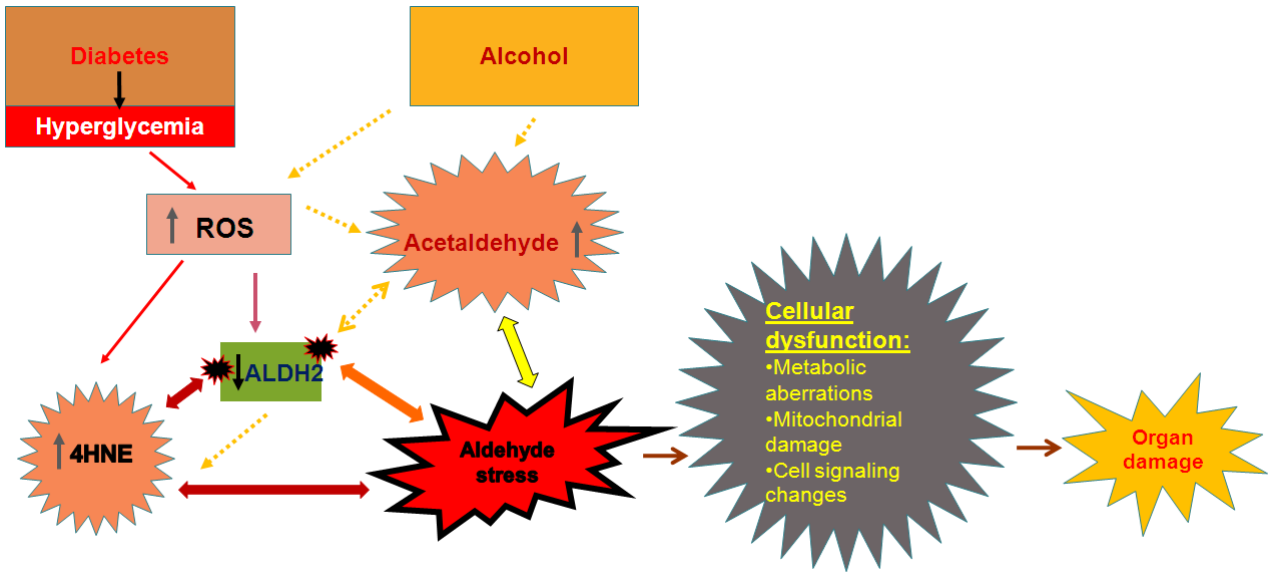

Fig. 2. Exacerbation of aldehyde stress in diabetics with alcohol toxicity. Diabetes-induced hyperglycemia-mediated reactive oxygen species (ROS) generates reactive aldehydes like 4-hydroxy-2-nonenal (4HNE). ROS and 4HNE decrease aldehyde dehydrogenase 2 (ALDH2) activity. Increased alcohol consumption result in excessive acetaldehyde levels and reduced ALDH2 activity. All of these changes lead to aldehydic stress, cellular dysfunction, and organ damage.

DEVELOPMENT OF NEW THERAPEUTIC TARGETS

The novel possible therapeutic targets should be the converging point between diabetes-induced toxicity and alcohol-induced toxicity at the metabolic, cell signaling, and pathophysiological levels (Fig. 2). For instance, we propose the axis of accumulation of reactive aldehydes (metabolic changes), inhibition of ALDH2 activity (cellular signaling), and mitochondrial dysfunction (pathophysiological changes) as the possible therapeutic targets. Reactive aldehydes are generated as a result of changes in metabolism of alcohol and high glucose-induced oxidative stress. Furthermore, ALDH2 activity influences the level of aldehydes in both conditions. This central problem lies in the fact that reactive aldehydes are known to induce mitochondrial dysfunction in both diabetes and alcohol toxicity. We call for new research initiatives to focus on the pathogenesis of the disease at multiple levels.

In conclusion, it is important to recognize the magnitude of "double trouble" epidemically as rates of both diabetes and alcohol toxicity are climbing. We described possible challenges in diagnosis, treatment, and management of the condition. Finally, we proposed potential strategy for identifying therapeutic targets.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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