

ALCOHOL EXACERBATES DYSLIPIDEMIA IN THE PREFRONTAL CORTEX OF DIABETIC RATS

ABSTRACT

Aim: To investigate the potential importance of the association between alcohol consumption, diabetes and increased dyslipidemia in the prefrontal cortex.

Study Design: Twenty-four adult rats were randomly divided into four groups of six rats each viz; Group 1- Control, given rat pellets and water *ad libitum*; Group 2- Diabetic, diabetes was induced with multiple dosage (120g/kg body weight) of alloxan. Group 3- Diabetic and low alcohol intake (9% w/w). Group 4- Diabetic and high alcohol intake (20% w/w).

Place and Duration of Study: This work was carried out in the Department of Anatomy; Olabisi Onabanjo University. Ago-Iwoye. Nigeria between February and April, 2012.

Methodology: The skull was dissected and the brain removed, the prefrontal cortex was excised, homogenized, centrifuged and the supernatant analyzed for lipid profile.

Results: The levels of ALT and AST were elevated in diabetes to 67.33 ± 0.15 and 135.50 ± 0.50 respectively. The tissue triglyceride level increased in diabetes from 72.62 ± 0.52 to 92.01 ± 0.18 , while total cholesterol and HDL decreased from 37.28 ± 0.23 and 150.90 ± 0.33 to 34.99 ± 0.04 and 103.32 ± 0.26 respectively. Alcohol intake on the other lowered the levels of all parameters significantly at $P=0.05$.

Conclusion: We concluded from our findings that both low and high chronic alcohol intake exacerbates the adverse effect of diabetes neuronal dyslipidemia.

Keywords: Diabetes; Alcohol; Lipids; Prefrontal cortex

24 **1.0 Introduction**

25 Numerous studies have demonstrated a J-shaped relationship between alcohol consumption and
 26 diabetes [1, 2]. Moderate consumption of alcohol is medically beneficial and socially acceptable
 27 [3], as moderate alcohol consumption also beneficially affects insulin sensitivity and glucose
 28 metabolism [4]. However, excessive consumption of alcohol leads to complex health problems,
 29 because alcohol may alter glycemic regulation and potentially aggravate the cardiovascular,
 30 neurological, and immunosuppressive changes in patients with diabetes mellitus. Because
 31 alcohol use, at least on a social level, is widespread among diabetics as well as non-diabetics,
 32 clinicians and researchers must understand alcohol's effect on the progression and complications
 33 of diabetes [5]. It is known that chronic alcoholics and type II diabetics show hyperlipidemia,
 34 characterized by hypertriglyceridemia and in a minor degree by hypercholesterolemia [6]. The
 35 most typical lipoprotein pattern in diabetes, also known as diabetic dyslipidemia or
 36 atherogenic dyslipidemia, consists of moderate elevation in triglyceride levels, low HDL
 37 cholesterol values, and small dense LDL particles. This lipoprotein pattern is associated with
 38 insulin resistance and is present even before the onset of diabetes. LDL cholesterol levels in type
 39 2 diabetic subjects are generally similar to those found in the general population. Small dense
 40 LDL particles are highly atherogenic because of their enhanced susceptibility to oxidative
 41 modification and increased uptake by the arterial wall [7]. The mechanisms underlying the effect
 42 of ethanol and carbohydrates on plasma lipids seem to be different; therefore in diabetic subjects
 43 chronic alcohol consumption could produce a more severe hyperlipidemia and so accelerate
 44 atherosclerotic events [6]. There are limited reports on the effect of alcohol during diabetic
 45 condition with reference to total cholesterol, triglycerides, high density lipoprotein in brain

tissue. Hence this study investigated the potential importance of the association between alcohol consumption, diabetes and dyslipidemia in the prefrontal cortex of the brain.

2.0 Materials and Methods

2.1 Experimental Animals

Twenty-four wistar rats, weighing (150g-170) were used for this study. The animals were housed in clean plastic cages, well ventilated environment with temperature ranging between 24-28°C in 12 hours light and 12 hours dark cycle. The animals were given standard rat pellets and water *ad libitum*, and were allowed to acclimatize for four weeks before commencing the experimental protocols. This research was conducted in accordance with the internationally accepted principles for laboratory animal use and care (NIH Publication: 83-23) [11].

2.2 Experimental Design

The rats were randomly divided into four groups of five rats viz;

Group 1- Control, given normal rat pellets *ad libitum* and water

Group 2- Diabetic, diabetes was induced with multiple dosages of 150mg/kg body weight of alloxan for a start and subsequently 50mg/kg body weight weekly till the end of the experiment.

Group 3- Diabetic and low alcohol consumption, the rats in this group received multiple dosages of alloxan (as in group 2). After establishing diabetes, they were given 9% w/w alcohol daily.

Group 4- Diabetic and high alcohol consumption, the rats received multiple dosages of alcohol (as in group 2), they were given 20% w/w alcohol.

67 Fasting blood glucose level and body weight of the animals were monitored regularly throughout
68 the duration of the experiment which lasted four weeks.

69

70 **2.3 Tissue sample preparation**

71 At the end of four weeks the rats were euthanized by administering 10g/kg body weight of
72 pentobarbital. The rats were then dissected and blood sample collected directly from the heart,
73 while the skull was cut open and the brain excised and a portion of the prefrontal cortex taken
74 homogenized and centrifuge at 3500rpm for 15minutes. The supernatant was collected for
75 biochemical analyses.

76 **2.4 Biochemical Analyses**

77 **2.4.1 Analyses of Lipid Parameters**

78 The Biochemical Parameters were assayed using the Randox kits

79 **2.4.1.1 High density lipoprotein (HDL)**

80 Procedure

81 The samples were pipetted into test tubes as outlined below:

	Reagent Blank	Standard	Sample
Distilled Water	100µl	-	-
Supernatant	-	-	100 µl
Standard Supernatant	-	100	-
Reagent	1000 µl	1000 µl	1000 µl

82 The mixture was incubated for 5 mins at 37°C. The absorbance of the sample and standard were measured against
83 the reagent blank within 60 mins, at a wavelength of 500nm.

84 2.4.1.2 Triglycerides

85 Procedure

86 The samples were pipetted into test tubes as outlined below:

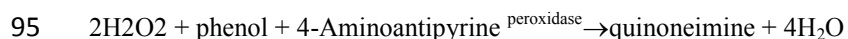
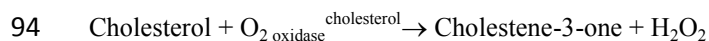
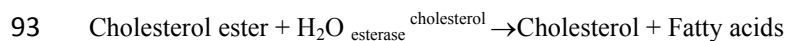
	Reagent Blank S0	Standard S1	Sample
ddH ₂ O	-	-	-
Standard	-	10 µl	-
Sample	-	-	10 µl
Reagent	1000µl	1000 µl	1.00 ml

87 The mixture was incubated for 5 mins at 37°C. The absorbance of the sample and standard were measured against
88 the reagent blank within 60 mins, at a wavelength of 500nm.

89 2.4.1.3 Cholesterol

90 Principle

91 The cholesterol is determined after enzymatic hydrolysis and oxidation. The indicator quinoneimine is formed from
92 hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxidase.



96 2.3.2 Procedure

97 The samples were pipetted into test tubes as outlined below:

	Reagent Blank S0	Standard S1	Sample
ddH ₂ O	10µl	-	-
Standard	-	10 µl	-
Sample	-	-	10 µl
Reagent	1000 µl	1000 µl	1.00ml

98 The mixture was incubated for 5 mins at 37°C. The absorbance of the sample and standard were measured against
99 the reagent blank within 60 mins, at a wavelength of 500nm.

100

101 2.4.1.4 Alanine Aminotransferase (ALT)

102 ALT was assayed using the Randox kits

103 Principle

104 α -oxoglutarate + L-alanine $\xrightarrow{\text{GPT}}$ L-glutamate + pyruvate

105 Alanine Aminotransferase is measured by monitoring the concentration of pyruvate hydrazone formed with 2, 4-
106 dinitrophenylhydrazine.

107

108 Reagent Composition

Contents	Initial Concentrations Of Solutions
R1. Buffer Phosphate buffer L-alanine α -oxoglutarate	100mmol/l, pH 7.4 200mmol/l 2.0mmol/l
R2. 2,4-dinitrophenylhydrazine	2.0mmol/l

109

110 Stability And Preparation Of Reagents

111 **R1. Buffer**

112 Contents ready for use. Stable up to expiry date when stored at +2 to +8°C.

113 **R2. 2, 4-dinitrophenylhydrazine**

114 Contents ready for use. Stable up to expiry date when stored at +2 to +8°C.

115 Procedure

116 Measurement against Reagent Blank

117 Pipette into test tubes:

	Reagent Blank	Sample
Sample	-	0.1ml
Solution R1	0.5ml	0.5ml
Distilled water	0.1ml	-

118 Mixed and incubated for exactly 30mins at 37°C

119	Solution R2	0.5ml	0.5ml
	Mixed and allowed to stand for exactly 20mins at 20 to 25°C		

120	Sodium Hydroxide	5.0ml	5.0ml
	Mixed, the absorbance of sample was read against the reagent blank after 5mins.		

121 Measurement against Sample Blank

122 Pipetted into test tubes

		Sample blank	Sample
	Sample	-	0.1ml
	Solution R1	0.5ml	0.5ml
123	Mixed and incubated for exactly 30mins at 37°C		

	Solution R2	0.5ml	0.5ml
	Sample	0.1ml	-
124	Mixed and allowed to stand for exactly 20mins at 20 to 25°C		

	Sodium Hydroxide	5.0ml	5.0ml
125	Mixed, the absorbance of the sample was read against the sample blank after 5mins.		

126 2.4.1.5 Aspartate Transaminase (AST)

127 AST was assayed using the Randox kits

128 Principle

129 α -oxoglutarate + L-aspartate $\xrightarrow{\text{GOT}}$ L-glutamate + oxaloacetate

130 AST is measured by monitoring the concentration of oxaloacetate hydrazone formed with 2,4-dinitrophenylhydrazine.

132 Reagent Composition

Contents	Initial Concentrations Of Solutions
R1. Buffer	
Phosphate buffer	100mmol/l, pH 7.4
L-aspartate	100mmol/l
α -oxoglutarate	2.0mmol/l
R2. 2,4-dinitrophenylhydrazine	2.0mmol/l

133 Stability And Preparation Of Reagents

134 **R1. Buffer**

135 Contents ready for use. Stable up to expiry date when stored at +2 to +8°C.

136 **R2. 2,4-dinitrophenylhydrazine**

137 Contents ready for use. Stable up to expiry date when stored at +2 to +8°C.

138 Procedure

139 Measurement against Reagent Blank

140 Pipette into test tubes:

	Reagent Blank	Sample
Sample	-	0.1ml
Reagent 1	0.5ml	0.5ml
Distilled water	0.1ml	-

141 Mixed and incubated for exactly 30mins at 37°C

Reagent 2	0.5ml	0.5ml
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142 Mixed and allowed to stand for exactly 20mins at 20 to 25°C

Sodium Hydroxide	5.0ml	5.0ml
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143 Mixed, the absorbance of sample was read against the reagent blank after 5mins.

144 Measurement against Sample Blank

145 Pipetted into test tubes

	Sample blank	Sample
Sample	-	0.1ml
Reagent1	0.5ml	0.5ml

146 Mixed and incubated for exactly 30mins at 37°C

Reagent 2	0.5ml	0.5ml
Sample	0.1ml	-

147 Mixed and allowed to stand for exactly 20mins at 20 to 25°C

Sodium Hydroxide	5.0ml	5.0ml
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148 Mixed, and the absorbance of the sample was read against the sample blank after 5mins.

149 Wavelength: 546nm

150

151 **2.4.1.6 Lipid peroxidation**

152 Malondialdehyde (MDA), an index of lipid peroxidation was determined using the method of Buege and Aust [26].

153 1.0 ml of the supernatant was added to 2 ml of (1:1:1 ratio) TCA-TBAHCl reagent (thiobarbituric acid 0.37%, 0.24N

154 HCl and 15% TCA) tricarboxylic acid thiobarbituric acid-hydrochloric acid reagent boiled at 100°C for 15 min, and

155 allowed to cool. Flocculent materials were removed by centrifuging at 3000 rpm for 10 minutes. The supernatant was

156 removed and the absorbance read at 532 nm against a blank. MDA was calculated using the molar extinction

157 coefficient for MDA-TBA complex of $1.56 \times 10^5 \text{ M}^{-1} \text{ cm}^{-1}$.

3.0 Results

3.1 Mean body weight in the experimental group

Figure 1 shows the mean body weights in the experimental groups. The body weights of control group dropped initially and then increase steadily, while the diabetic group witnessed consistent dropped. Both high and low chronic alcoholintakes improve body weight in diabetic rats.

3.2 Mean level of Triglycerides, total cholesterol and high density lipoprotein in the prefrontal cortex

Fig 2 shows that both diabetes and alcohol lowered high density lipoprotein (HDL) total cholesterol significantly at ($P= 0.05$), while triglycerides level was significantly increased by diabetes. Alcohol intake exacerbates the effect of diabetes.

Table 1: Compares the triglycerides levels in all experimental groups. Diabetes increased significantly ($P< 0.05$) the level triglycerides in the prefrontal cortex; while alcohol lowered the level with more significantly decrease in the low alcohol intake.

Table 2: Compares the cholesterol levels in all experimental groups. Diabetes significantly ($P< 0.05$) lowered the total cholesterol level in the prefrontal cortex; while low alcohol intake lowered the cholesterol level more than in high alcohol intake group.

Table 3:Compares the high density lipoprotein levels in all experimental groups. Diabetes significantly ($P< 0.05$) lowered the high density lipoprotein level in the prefrontal cortex; high alcohol intake lowered the high density lipoprotein level more than in low alcohol intake group.

Table 4: Compares the Alanine aminotransferase(ALT) levels in all experimental groups. Diabetes increasedsignificantly ($P< 0.05$) the level ALT; in the same vein alcohol intake in diabetics also lowered the level with more significantly decrease in the low alcohol intake.

Table 5: Compares the Aspartate transaminase (AST) levels in all experimental groups. Diabetes increased significantly ($P < 0.05$) the level ALT; in the same vein alcohol intake in diabetics also lowered the level with more significantly decrease in the high alcohol intake.

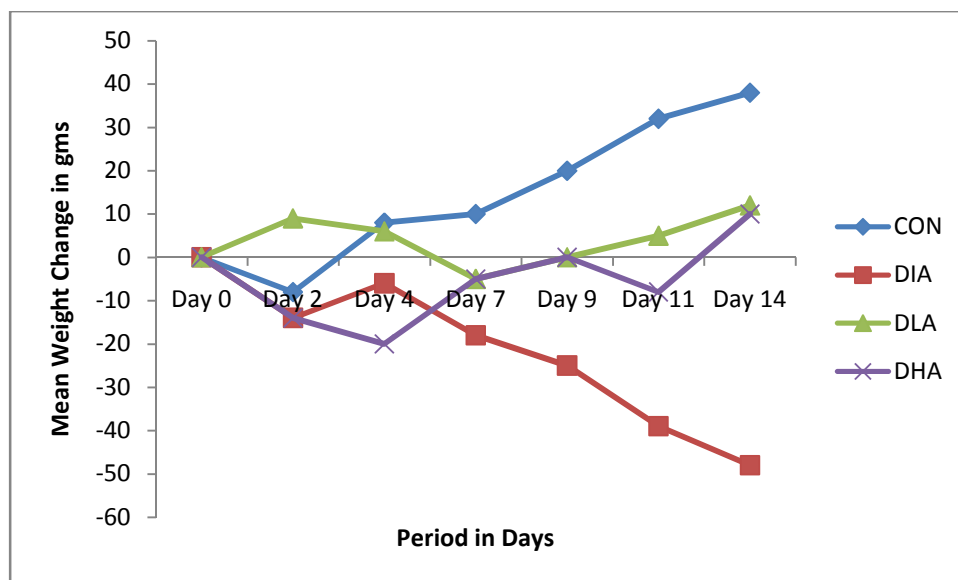


Figure 1: mean weight change in experimental groups (CON=Control; DIA=Diabetic; DLA=Diabetic and Low Alcohol; DHA=Diabetes and High Alcohol)

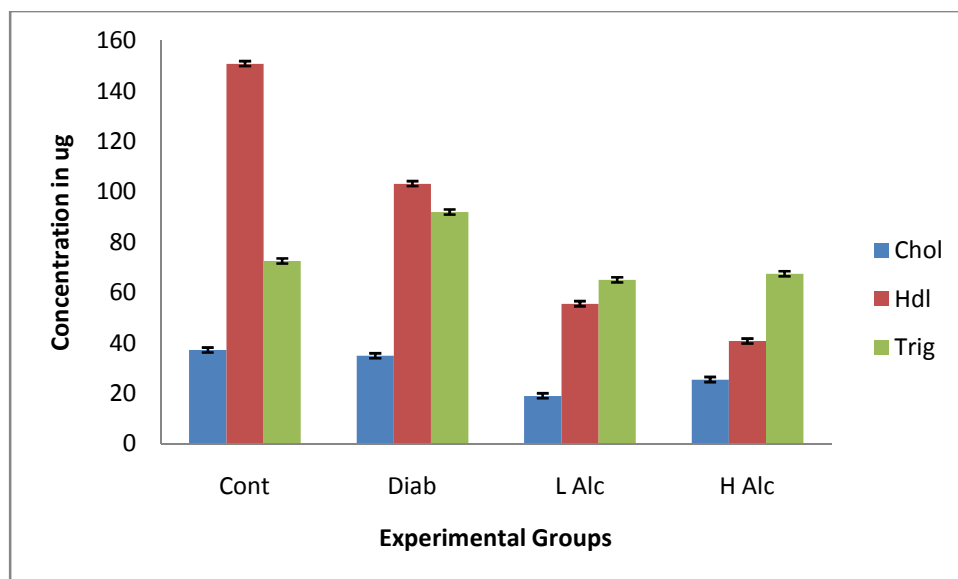


Figure 2: lipid concentration in the prefrontal cortex of Cont=Control; Diab=Diabetic;

194 L Alc=Low Alcohol; H Alcohol

195

196 TABLE 1: Mean level of triglycerides in the prefrontal cortex

GROUP	Mean±SE	p-Value
NORMAL CONTROL	72.62±0.52	0.002
UNTREATED DIABETIC	92.01±0.18	
NORMAL CONTROL	72.62±0.52	0.059
DIABETIC + LOW ALCOHOL	65.14±0.43	
NORMAL CONTROL	72.62±0.52	0.014
DIABETIC + HIGH ALCOHOL	67.53±0.22	
UNTREATED DIABETIC	92.01±0.18	0.015
DIABETIC + LOW ALCOHOL	65.14±0.43	
UNTREATED DIABETIC	92.01±0.18	0.001
DIABETIC + HIGH ALCOHOL	67.53±0.22	
DIABETIC + LOW ALCOHOL	65.14±0.43	0.152
DIABETIC + HIGH ALCOHOL	67.53±0.22	

197 *P value is significant at p=0.05*

198

199 TABLE 2: Mean level of cholesterol in the prefrontal cortex

200

GROUP	Mean±SE	p-value
NORMAL CONTROL	37.28±0.23	0.169
UNTREATED DIABETIC	34.99±0.40	
NORMAL CONTROL	37.28±0.23	0.003
DIABETIC + LOW ALCOHOL	19.10±0.30	
NORMAL CONTROL	37.28±0.23	0.006
DIABETIC + HIGH ALCOHOL	25.56±0.32	
UNTREATED DIABETIC	34.99±0.40	0.028
DIABETIC + LOW ALCOHOL	19.10±0.30	
UNTREATED DIABETIC	34.99±0.40	0.034
DIABETIC + HIGH ALCOHOL	25.56±0.32	
DIABETIC + LOW ALCOHOL	19.10±0.30	0.018
DIABETIC + HIGH ALCOHOL	25.56±0.32	

201 ***P value is significant at p=0.05***

202

203 TABLE 3: Mean level of high density lipoprotein in the prefrontal cortex

GROUP	Mean±SE	p-value
NORMAL CONTROL	150.90±0.33	0.008
UNTREATED DIABETIC	103.29±0.26	
NORMAL CONTROL	150.90±0.33	0.002
DIABETIC + LOW ALCOHOL	55.66±0.27	
NORMAL CONTROL	150.90±0.33	0.001
DIABETIC + HIGH ALCOHOL	40.83±0.30	
UNTREATED DIABETIC	103.29±0.26	0.003
DIABETIC + LOW ALCOHOL	55.66±0.27	
UNTREATED DIABETIC	103.29±0.26	0.008
DIABETIC + HIGH ALCOHOL	40.83±0.30	
DIABETIC + LOW ALCOHOL	55.66±0.27	0.021
DIABETIC + HIGH ALCOHOL	40.83±0.30	

204 ***P value is significant at p=0.05***

205 Table 4: Mean level of Alanine aminotransferase(ALT) Levels

GROUP	Mean±SE	p-value
NORMAL CONTROL	59.25± 0.25	0.008
UNTREATED DIABETIC	67.33±0.15	
NORMAL CONTROL	59.25±0.25	0.002
DIABETIC + LOW ALCOHOL	24.48±0.28	
NORMAL CONTROL	59.25±0.25	0.005
DIABETIC + HIGH ALCOHOL	26.63±0.18	
UNTREATED DIABETIC	67.33±0.15	0.001
DIABETIC + LOW ALCOHOL	24.48±0.28	
UNTREATED DIABETIC	67.33±0.15	0.008
DIABETIC + HIGH ALCOHOL	26.63±0.18	
DIABETIC + LOW ALCOHOL	24.48±0.28	0.133
DIABETIC + HIGH ALCOHOL	26.63±0.18	

225 ***P value is significant at p=0.05***

226

227 Table 5: Mean activities of Aspartate transaminase(AST) levels

228	GROUP	Mean±SEp-value	
229	NORMAL CONTROL	75.50± 0.50	0.011
230	UNTREATED DIABETIC	135.50±0.50	
231			
232	NORMAL CONTROL	75.50±0.50	0.019
233	DIABETIC + LOW ALCOHOL	73.85±1.35	
234			
235	NORMAL CONTROL	75.50±0.50	0.006
236	DIABETIC + HIGH ALCOHOL	60.25±0.25	
237			
238	UNTREATED DIABETIC	135.50±0.50	0.013
239	DIABETIC + LOW ALCOHOL	73.85±1.35	
240			
241	UNTREATED DIABETIC	135.50±0.50	0.010
242	DIABETIC + HIGH ALCOHOL	60.25±0.25	
243			
244	DIABETIC + LOW ALCOHOL	73.85±1.35	0.051
245	DIABETIC + HIGH ALCOHOL	60.25±0.25	
246	<i>P value is significant at p=0.05</i>		

247

248

249

250 4.0 Discussion

251 The body weight showed an initial drop within the first week of treatment followed by
 252 subsequent increase in the alcohol intake groups, while the diabetic group showed steady
 253 decrease.The alcohol induced increase concurs with the work conducted by Frederick Grant
 254 Banting [8] who attributed the increase to the fact that alcohol adds empty calories to diet.
 255 Diabetes mellitus is characterized by hyperglycemia together with biochemical alterations of
 256 glucose and lipid peroxidation [9] [10]. The mechanisms underlying the effect of ethanol and
 257 carbohydrates on plasma lipids seem to be different.In the present study diabetes was

258 characterized by significant hypertriglycerides and hypocholesterol in the prefrontal cortex while
259 alcohol ingestion in diabetic rats significantly lowered brain tissue triglycerides and cholesterol.

260
261 There exists an association between diabetes and liver injury. Liver plays a major role in the
262 regulation of carbohydrate homeostasis. Hepatocellular glycogen accumulation leads to
263 hepatomegaly and liver enzyme abnormalities in poorly controlled diabetes patients. In
264 hyperglycemic states, there will be intracellular glycogen accumulation in the hepatocytes due to
265 increased glycogen synthesis, causing typical biochemical findings of mild to moderately
266 elevated aminotransferases as reported in this study by the significant elevation in the levels of
267 ALT and AST in diabetic rats due to tissue compromise and increased physiological needs. ALT,
268 produced mainly in the liver, catalyzes the transfer of amino groups between L-alanine and
269 glutamate to meet physiological needs. AST catalyzes the transfer of amino and keto groups
270 between alpha-amino acids and alpha-keto acids thereby acquiring the term transferase [11].
271 Alcohol seems to not only to reverse this effect but lower the levels below the control level
272 probably by immuno-depletion of ALT1 which decreases majority of the serum ALT activity in
273 healthy humans [12], while alcohol intake lowered the enzymes levels..

274
275 The hypertriglycerides noticed in the diabetic group agrees with previous reports[13,14,15]. The
276 increase could be due to the increased in lipid peroxidation, a free radical-related process, is an
277 uncontrolled, self-enhancing process causing disruption of membranes, lipids and other cell
278 components. Unlimited lipid peroxidation (LP) could be one of the main factors in the
279 pathogenesis of diabetic complications. This pathology is often related to the release of free
280 radicals which cause oxidative stress [16]. During reoxygenation, hypoxanthine-xanthine oxidase

281 and arachidonic acid pathways are important sources of free oxygen radicals, which damage lipid
 282 membranes, and lead to cytolysis and cell death [17]. Accumulation of lipids in diabetes is
 283 mediated through a variety of derangements in metabolic and regulatory processes, especially
 284 insulin deficiency, thereby rendering the diabetic patient more prone to hypertriglyceridemia.
 285 Our results also showed that the total cholesterol level was significantly decreased in the
 286 prefrontal cortex.

287
 288 The brain being the most cholesterol-rich organ in the body, most of which comes from in situ
 289 synthesis [18]. Brain cholesterol turnover is increased in Alzheimer's and other
 290 neurodegenerative diseases, and has been suggested to play a role in pathogenesis of these
 291 disorders [19]. Diabetes mellitus is associated with a variety of neurologic and cerebral
 292 complications, including cognitive dysfunction, depression, and increased risk of Alzheimer's
 293 disease [20, 21, and 22]. The hypocholesterolemia reported in this study could be explained by
 294 the high insulin levels caused by diabetes which impair insulin signaling in the brain and affect
 295 lipid metabolism [23]. It is also characterized by decreased sensitivity and resistance to insulin
 296 [24]. Previous report indicates that chronic alcohol abuse causes a Type 2 diabetes effect in
 297 certain brain regions. Investigations on human tissue show that high levels of chronic alcohol
 298 consumption lower the levels of genes needed to respond to insulin and insulin growth factor
 299 (IGF) resulting in brain damage [24]. Apart from effects on lipid metabolism, haemostatic
 300 balance and blood pressure, alcohol improves insulin sensitivity. This improvement of insulin
 301 sensitivity may also be responsible for the lower incidence of type 2 diabetes mellitus reported to
 302 be associated with light-to-moderate drinking [25]. Ethanol-induced perturbations in membrane
 303 lipid composition contribute to insulin/IGF resistance in brain. One possible explanation is that,

304 besides cholesterol, ethanol depletes a variety of membrane lipids. In this study, diabetes and
 305 alcohol seemed to have a common pathway for the down regulation lipid biosynthesis pathway
 306 in the prefrontal cortex of treated rats. These have been associated with a change in gene
 307 expression which leads to a decrease in cholesterol synthesis in brain and a decrease in
 308 cholesterol content in synaptosomal membranes. Mimicking the reduction in
 309 cholesterologenic genes in cultured neurons by knockdown of SREBP-2 results in reduced
 310 markers of synapse formation, and knockdown of SREBP-2 in the hypothalamus in vivo causes
 311 altered feeding behavior and dysregulation of counterinsulin hormones [26]. Over the past decade
 312 there have been important advances in defining the mechanisms that cells use to regulate
 313 cholesterol levels and lipid metabolism [27]. In liver and kidney, insulin has been shown to
 314 activate both SREBP-1 and SREBP-2 [28,29], which in turn control both fatty acid and
 315 cholesterol biosynthesis. Our results indicate that this same system may play an important role in
 316 control of brain cholesterol and triglycerides levels with direct regulation by insulin of SREBP-2
 317 and down-stream cholesterologenic genes at the transcriptional level leading to altered rates of
 318 cholesterol biosynthesis. There is a strong feedback system in which cholesterol and sterol
 319 intermediates regulate the activation of the SREBP family of transcription factors through
 320 mechanisms involving ER-to-Golgi transport and production of the active transcription factor
 321 through limited proteolysis [27]. While it is likely that this feedback system is active in brain, in
 322 the brain of diabetic animals, there is a failure to compensate for reduced cholesterol synthesis
 323 and reduced synaptosomal cholesterol with up-regulation of cholesterologenic genes. This might
 324 be due to morphological complexity of neurons and astrocytes that have long processes spatially
 325 distant from the endoplasmic reticulum, where SREBP cleavage-activating protein (SCAP)

works as a sensor, or might represent a fundamental difference in regulation of cholesterol synthesis in brain and liver.

328

329 CONCLUSION

From our findings both low and high chronic alcohol intake exacerbates the adverse effect of diabetes neuronal dyslipidemia, by lowering ALT and AST levels or via the mechanism that suppresses the enzymes of lipid syntheses in the prefrontal cortex, leading to reduction in synaptic membrane cholesterol, and altered neuronal and physiological function.

334

335 CONSENT

Not applicable.

337 COMPETING INTERESTS

Authors have declared that no competing interests exist

339

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341

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343 alcohol consumption, health indicators and mortality in the german population. Int J
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