Modulation of Hormonal, Oxidative Stress and Fatty Acids Profiling in Response to Glutamine and Chromium in Diabetic Rats

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Background: Fatty acids profiling of diabetes may be helpful in early diagnosis and management of diabetic. Chromium is a trace element and important cofactor for many anti-oxidant enzymes as superoxide dismutase. Glutamine is semi essential amino acid and reported to improve endothelial function, decrease blood pressure, and vasodilator. This study investigated fatty acids profiling in diabetic rats and their response to administration of glutamine and chromium.

Methods: Fifty male albino rats were divided into 2 groups as following: GPI (10 rats); Control group. GP II (40 rats) were injected alloxan (75 mg /kg) i.p. for six consecutive days for induction of diabetes. Diabetic rats were divided into four groups: GP II: (Untreated diabetic): GP III: Rats were given orally with L-glutamine (100 mg/kg).GP IV: Rats were given with Chromium chloride (30 µg/kg) ip. GP IV: Rats were given Glutamine and Chromium. After 6 weeks. Sera were used for the determination of Nitric oxide (NO), malondialdehyde (MDA), total antioxidants, insulin, glucagon, HA_C and fatty acids profile.

Results: Data obtained showed that, diabetic rats treated with glutamine and chromium restore the levels of hormones, HA_C, NO and MDA better than individual treatment (p<0.01) compared with untreated diabetic (p<0.001). A significant elevation of saturated fatty acids in diabetic and reduced...
unsaturated FA compared with control. Combination treatment reversed this ratio. This may explain increased insulin sensitivity in treated rats compared with untreated. **Conclusion:** It was concluded that, Glutamine combined with chromium increased insulin sensitivity and recovery pancreatic efficacy in insulin production. Administration of glutamine or chromium reduced HA1c, the mechanisms involved explored the potential of these compounds in control fatty acids contents and management of diabetic.

**Keywords:** Fatty acids; glutamine; chromium; diabetic; rats.

1. INTRODUCTION

Diabetic is considered as the most health problem worldwide. Most research focusing on the decrease prevalence of disease by early predication or minimize its complications that increase morbidity and mortality [1].

Metabolomics is a new research trend to discover different metabolites in different cases (normal and diseases) in biological fluids to use as diagnostic or prognostic or choose therapeutic protocol [2]. This is allowing an accurate and rapid identification about that disease. Metabolomics strategies present several practical advantages, including being relatively low cost per sample, high throughput and fully automated [3]. Metabolomics profiling of diabetes relate to two different stages of the disease in order to see whether metabolomics profiling might be an early diagnostic and prognostic biomarkers for diabetic and the candidate were most deregulated that might be the basis of biomarker for the disease therapies that intend to correct metabolic deregulation must be patient based [4].

Chromium is a trace element and important cofactor for many anti-oxidant enzymes as superoxide dismutase, and its deficiency interfere there with synthesis, that lead to increased free radicals release [5]. It was reported that, diabetes is associated with by decreased chromium level [6]. Glutamine is semi essential amino acid and reported to improve endothelial function, decrease blood pressure and vasodilator .Glutamine improved endothelial function by decreased synthesis of cytokines and prostaglandins [7].

The life styles and food type could affect the metabolomic deregulation and hence affect disease stages that reflect metabolomic profiling. However, we do not know whether the biomarkers found from these metabolomic research could also be applied on Saudi patients due to differences in life styles and nature of food .This is could be to justify obtaining serum as a tool for early detection of diabetes [8]. In this study we investigated fatty acids profiling that has been secondarily affect and could a biomarker for the disease but substantially for those which are behind or associated with the diabetic treated with glutamine and or with chromium. This promising in help a lot in understanding the etiopathogenesis of the disease from a metabolomics. It would give a treasure of metabolites that could cover the theses of many investigators.

2. MATERIALS AND METHODS

The handling with animals were done according to Ethical Committee of King Abdulaziz University. Fifty male albino rats were included in this study weight 200 ± 20 g . Rats were divided into two groups as following: (GP1; 10 rats); control group which were received a single dose of 0.1 µmol/l citrate buffer only. GP II (40 rats); The remaining rats were injected alloxan (75 mg /kg) i.p. for six consecutive days. These animals were developed within three weeks .Diabetic rats were divided into four groups (each 10 rats) as follows: GP II: (Untreated diabetic); GP III: Rats were given orally with L-glutamine (100 mg/kg) GP IV: Rats were given with Chromium chloride (30 µg/kg) i.p GP IV: Rats were given with Glutamine and Chromium. At the end of the experiments (6 weeks). Blood was collected directly from all groups. Serum was separated and used for the determination of NO, MDA, total antioxidant, HA1C, glucagon, insulin by using kits from Biodiagnostic, England. Free fatty acidswas determined by Gas chromatography/ mass spectrum.

2.1 GC-MS Analysis of Fatty Acids Methyl Esters

The GC-MS analysis of fatty acids methyl esters of serum were performed according to Adams (1995) with a Finnigan Mat SSQ 7000 gas
chromatography coupled to mass detector belong to NRC. Compounds of the different fatty acids were identified by their retention times (RT) and interpretation of their mass spectra.

2.2 Statistical Analysis

Results were statistically analyzed using SPSS version 21, one-Way ANOVA, p<0.05 was considered as significant. Correlation study using pearson test.

3. RESULTS

Fig. 1 the levels of MDA and NO were significantly increased in diabetic (P<0.01). This high level of MDA and NO were reduced as a result of glutamine and chromium treatment (P<0.001). Total antioxidant level was recovered in response to administration of glutamine and chromium compared with untreated diabetic (Fig 2).

Rats injected with alloxan caused partial damage of pancreatic β cells that reduced insulin and elevated glyacted hemoglobin compared with control. Treatment with glutamine or chromium protected this partial damaged and enhances insulin action that decreased HA1c. The effect of chromium is better than glutamine (Fig. 3).

Partial damage of pancreatic cell caused alteration in hormones secretion followed by reduced insulin (p<0.001) and non-significant changes in glucagon compared with control. Treatment of diabetic rats with glutamine or chromium attributed to the anti-oxidative and anti-inflammatory effects of both and restore insulin level compared with untreated diabetic rats. The effect of chromium is better than glutamine (p<0.05) (Fig. 4).

3.1 Fatty Acids Composition

Fig (5) showed the retention time of standard fatty acids including saturated and unsaturated fatty acids. The identification of individual fatty acids in serum were carried out and presented in Table 1. The peaks related to different fatty acids at different retention times (RT) were shown in Fig. 5, some of these peaks were detected and identified, while others about (3.43%) were unidentified. Results in Table 1 showed that 7 fatty acids were identified and detected in serum, some of these fatty acids were saturated represented (13.26% of total fatty acids) as palmitic and stearic and the

![Graph showing NO and MDA levels in different groups](image-url)

**Fig 1.** The levels of NO and MDA in different studied groups

<table>
<thead>
<tr>
<th></th>
<th>NO (ug/ml)</th>
<th>MDA (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diab+Glutamine</td>
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<tr>
<td>Diab+Chromium</td>
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<tr>
<td>Diab+Glutamine+Chromium</td>
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most predominant saturated fatty acid was palmitic acid (7.64%). Five unsaturated fatty acids were detected including palmitoleic, oleic, linoleic, γ-linolenic and arachidonic acid. Total unsaturated fatty acids represented (83.31% of total fatty acids composition). The unsaturated linoleic acid represented the majority of total fatty acids composition (34.23%) followed by γ-linolenic (24.79%) and oleic acid (14.23%). In diabetic rats the% of saturated is higher than unsaturated compared with control. Treatment with either glutamine or chromium reversed this ration by elevating linoleic and linolenic acids compared with untreated diabetic.

Fig 2. The activity of total antioxidant in different studied groups

Fig 3. The level of HA1c in different studied groups
Fig 4. The levels of serum insulin and glucagon in different studied groups

Fig 5. GC-MS of fatty acids profile

4. DISCUSSION

Metabolomics is a new focusing research that aid in diagnosis and management of different diseases by altering these intermediate. Detection of novel biomarkers and mechanisms related to the development of insulin resistance (IR), type 2 diabetes (T2D), and diabetic complications and in helping to understand the mechanism of action of diabetes therapies [9]. The pathophysiology and useful data for risk prediction and developing effective therapeutic and preventive strategies against diabetes are provided by the description of metabolic profiles and perturbed metabolic pathways which involved in T2D development [10,11]. Several plasma metabolites are involved in glycolysis/gluconeogenesis and metabolisms of branched amino acids [12]. Previous study showed that, glutamine is a vital amino acid that
Table 1. Serum free fatty acids profile as a percentage concentrations of total fatty acids

<table>
<thead>
<tr>
<th>Fatty acids</th>
<th>RT (Standard)(min)</th>
<th>GPI (%)</th>
<th>GPII (%)</th>
<th>GPIII (%)</th>
<th>GPIV (%)</th>
<th>GPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saturated FA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>22.34</td>
<td>7.64</td>
<td>7.64</td>
<td>7.64</td>
<td>7.64</td>
<td>7.64</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>26.16</td>
<td>3.08</td>
<td>3.08</td>
<td>3.08</td>
<td>3.08</td>
<td>3.08</td>
</tr>
<tr>
<td><strong>Unsaturated FA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>15.48</td>
<td>34.23</td>
<td>34.23</td>
<td>34.23</td>
<td>34.23</td>
<td>34.23</td>
</tr>
<tr>
<td>Arachidic acid</td>
<td>8.90</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>γ-Linolenic acid</td>
<td>19.16</td>
<td>2.06</td>
<td>2.06</td>
<td>2.06</td>
<td>2.06</td>
<td>2.06</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>31.28</td>
<td>1.69</td>
<td>1.69</td>
<td>1.69</td>
<td>1.69</td>
<td>1.69</td>
</tr>
</tbody>
</table>

RT: Retention time; GPI: Control; GPII: Diabetic; GPIII: Diabetic + Glutamine; GPIV: Diabetic + Chromium; GPV: Diabetic + Glutamine + Chromium

play important roles as detoxification of urea and synthesis of glutathione. In this study MDA and NO elevated in response to alloxan injection. As showed in previous study, alloxan induce release of free radicals as NO and increased lipid peroxidation as indicated by elevation of MDA [13-15].

The MDA level, is a biomarker of fat oxidation by free radicals which it was increased in diabetic untreated rats. The results of the present study are similar to those of a previous study of a alloxan induced diabetic rat model [16]. It had been reported that glutamine and chromium have anti-oxidant as indicated by the elevation in antioxidant efficacy and decreased MDA and NO levels diabetic rats treated with either glutamine or chromium. This is accompanied by modulation of insulin level as it was reduced in alloxan treatment and restored in treatment with glutamine and chromium.

Previous study reported that, chromium give in diabetes subjects may showed positive effect on glycemia and hyperlipidemia [5].

It was found that, unsaturated FA is one was associated with a significant 69% reduced risk of T2D which contains linoleic and linolenic acids. Whereas metabolite factor two was associated with a significant increased the risk of T2D which contains saturated fatty acids and insulin resistance [17]. The evidence of an association between saturated fatty acids (SFAs) and type 2 diabetes are discordant. There is a correlation between SFAs in the plasma with the risk of T2D. The study revealed that even-chain SFAs (palmitic acid 16:0 and stearic acid 18:0) were positively correlated with the incidence of T2D while odd-chain SFAs and longer-chain SFAs were inversely associated with T2D [18]. Obesity and insulin resistance strongly predispose to type 2 diabetes mellitus. The relationships among measures of IR and amino acid and fatty acid metabolism differ strikingly according to gender. Furthermore, obese subjects also showed altered in β-oxidation and altered urinary excretion of dicarboxylic acids as well as reduced levels of tetradecenoyl carnitine (C14:2) only when dysglycemic, indicating the differential involvement of the metabolic pathways [19]. A negative correlation between insulin level and glycated hemoglobin (HbA1c).

It was reported that glutamine caused elevation of GLP-1 secretion in normal subjects [9] or type 2 diabetes [20]; In addition GLP-1 enhance production of insulin secretion via an incretin effect, GLP-1 also stimulate glucose metabolism [15].

Different lifestyle factors and phenotypes are reflected in metabolic pathways. Fatty acids profile in diabetic rats showed elevated saturated (palmitic and stearic acids) than unsaturated Linoleic and linolenic acids) compared with control. Previous study shoed that, saturated FA accompanied with insulin resistance and increase HA1c.

Palmitic acid, palmitoleic acid, and others six lipids/fatty acids were elevated in T2D [20,21], all positively associated with impaired glucose tolerance and T2D [22-25]. Treatment with glutamine and chromium improve the ratio between saturated and unsaturated and lead to improve HA1c level.

5. CONCLUSION

In conclusion, it was deduced that, glutamine and chromium showed anti-oxidative and
hypoglycemic, reduce NO• and enhance the total antioxidant activity. Further detailed mechanistic studies are necessary to unveil the beneficial role of these compounds as a useful natural, anti-diabetic antioxidant.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The handling with animals was done according to Ethical Committee of King Abdulaziz University.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES


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