EFFECTS OF ACCIDENTAL ANTIHYPERGLYCEMIC OVERDOSES ON LYSOSOMAL ENZYMOLGY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

By


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ABSTRACT

Background: Quantitative estimation of lysosomal enzymes in the blood reflect the pathophysiological state of the intracellular lysosomes and subsequently the mother cells. Aim: To assess the effect of induced hypoglycemia due to accidental intake of antihyperglycemic drugs (insulin and/or sulfonylurea) overdoses by type-2 diabetic patients on some serum lysosomal enzymes. These are reliable markers of the intracellular lysosomal bioactivities and long-term cell lifespan. Subjects and Methods: Thirty type-2 diabetic patients suffering from severe hypoglycemia because of accidental overdose intake of insulin injection (8 patients), sulfonylurea ingestion (10 cases) or both drugs together (12 patients) due to drug automation and/or missed or disproportionate meal. At the same time, 15 patients with controlled DM, 15 patients with uncontrolled DM and 10 healthy reference individuals were studied. All these groups were almost of matched age, sex and body weight. Blood samples were withdrawn after breakfast and the designated antihyper-glycemic intake. Beside, plasma glucose, three serum acidic lysosomal enzymes i.e. the carbohydrazde: BN acetyl glucosaminidase (B-NAG), the protease: cathepsin-D (CATH-D) and the monophosphoric ester hydrolase: non-prostatic acid phosphatase (NPAP) were determined by the respective colorimetric method. Results: Accidental intake of insulin injection and/or oral antihyperglycemic drugs in overdoses induced significant increase of the estimated serum lysosomal enzymes. In this respect, the response to insulin was higher but shorter than that by sulfonylurea intoxication. At the same time, B-NAG had higher response than CATH-D and NPAP to the antihyperglycemic drug overdoses. There was no significant correlation between plasma glucose concentrations and the estimated serum lysosomal enzyme activities in the different studied groups. The results of the controlled euglycemic diabetics were significantly lower than those in the hypoglycemic group but not significantly different from those in the healthy group. At the same time, the results of the uncontrolled diabetics were significantly lower than those in the hypoglycemic group but significantly higher than the respective values of the healthy refer-
unless dextrose is promptly and adequately administered (Granner, 2000). Insulin self poisoning is rare. Its prognosis relies on clinical findings and time of initiation of management. About 16% of patients developed severe hypoglycemia, half of them died (Megarban et al., 2007).

Lysosomes are intracytoplasmic organelles that contain different acid hydrolases (optimum pH 4.0) which comprise lipases, carbohydrases, proteases and others. They are the intracellular garbage system that degrade the intracellular bacteria and worn out organelles. Lysosomes are frequently nicknamed "suicide-bags" or "suicide-sacs" due to their role in autolysis. Small cell amounts of lysosomal enzymes are normally released into the extracellular milieu. They are inactive at the normal blood pH (7.3-7.4). However, in some cases larger amounts are released into blood due to pathophysiological or genetically determined lysosomal disorders (Junqueira et al., 2005; Maehr et al., 2005; van Meel and Klumperman, 2008).

Key Words: Bn Acetyl Glucosaminidase, Cathepsin-d, Non-prostatic Acid Phosphatase, Body Mass Index, Antihyperglycemics, Type 2 Diabetes Mellitus.

INTRODUCTION

Management of patients with type 2 diabetes mellitus usually involved combined pharmacological therapy to obtain adequate blood glucose control and treatment of concurrent pathologies particularly dyslipidemia and arterial hypertension. Antidiabetic medications include insulin compounds given parenterally and insulin secretagogues given orally. In management of type 2 DM, oral antihyperglycemics should be tried before insulin therapy is allowed (Scheen, 2005). Antihyperglycemic therapy aims to normalize the diabetic metabolic anomalies and subsequently prevents or reduces morbidity and mortality caused by the relatively common serious diabetic complications (Riley and Kastrup, 2001).

Hypoglycemia may occur if the antihyperglycemic therapy is more than really required, there is a missed meal after the intake of the recommended therapy or after unplanned physical or mental stress. Severe hypoglycemia may lead to death unless dextrose is promptly and adequately administered (Granner, 2000). Insulin self poisoning is rare. Its prognosis relies on clinical findings and time of initiation of management. About 16% of patients developed severe hypoglycemia, half of them died (Megarban et al., 2007).

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Diabetic patients had higher concentrations of blood lysosomal enzymes e.g., BN acetyl glucosaminidase (B-NAG) (Agardh et al., 1991). The circulating lysosomal enzyme changes in diabetics arise by their leakage from damaged tissues (Waters et al., 1992). Recently it has been reported that only plasma N-acetyl-beta-D-glucosaminidase (B-NAG) but not cathepsin B activities showed higher values in type 2 diabetic patients (Piwowar et al., 2006). Moreover, type 1 diabetic patients showed significantly higher fraction β form and lower A fraction form in total NAG (Jovanovic et al., 2008). The underlying cause of high plasma lysosomal enzyme concentrations is the increased lysosomal fragility and rupture due to increased lipid peroxidation of the lysosomal membrane (George, 2008). On the other hand, total NAG activities in NIDDM with or without complications were not changed considerably compared to the control group (Mandic and Filipovic, 1998).

Insulin is involved in the regulation of lysosomal biology (Duckworth et al., 1998; Granner, 2000). In this respect, insulin showed biphasic activities since in young rats, it suppressed lysosomal proteases activities while in old rats, insulin increased the activity of these lysosomal enzymes (Gromakova and Konovalenko, 2003). Lysosomal enzyme bioactivities are regulated in a glucose-independent way (Gromokova and Konovalenko, 2003).

Sulfonylureas and their analogues are currently a key in the pharmacological management of type 2 DM. Sulfonylureas are insulin secretagogues by which they mandate their anti hyperglycemic function that allows the achievement of their glucose metabolic targets (Tian et al., 1998; Scheen, 2005). Oral antidiabetic medications pose a significant morbidity and permanent sequelae and even mortality secondary to their accidental overdoses producing prolonged and severe hypoglycemia. However, prognosis is usually good if intervention using 50% dextrose polus followed by 10% glucose infusion is initiated early (Spiller and Sawyer, 2006).

Few and mostly experimental works on antidiabetic overdose induced hypoglycemic effects on lysosomal enzyme activities has been reported (Gromokova and Konovalenko, 2003) and their results present obvious controversy.

Aim of this research was to determine the effect of accidental intake of insulin and/or sulfonylurea in overdoses on serum concentration of some lysosomal enzymatic activities [the carbohydrase; B-NAG; the protease : CATH-D, and the monophosphoric ester hydrolase NPAP] in patients with type 2 DM.
SUBJECTS and METHODS

(1) Hypoglycemic diabetic patient group:
This group included 30 patients with type 2 DM. They were of medium build and age and free of chronic diabetic complications. These diabetic patients were receiving orally one of the sulfonylurea drugs (glibenclamide, gliclazide) and/or human insulin (the intermediate neutral protamine Hagedorn [NPH]) injection. All these patients were admitted to the Special Internal Medicine or the Emergency Hospitals of Mansoura University with severe hypoglycemia due to overdose injected insulin (8 patients), ingested sulfonylurea (10 cases) or both drugs (12 patients) beside missed meal intake, or severe stressful environment. Exclusion criteria were (i) Endocrinal disorders: pituitary, adrenal cortex, thyroid and/or gonadal dysfunctions. (ii) Smoking (more than 20 cigarettes/day) and (iii) Current treatment with drugs interfering with the antidiabetic therapy such as steroids.

(2) Euglycemic diabetic patients: 15 patients with controlled DM due to treatment by sulfonylurea, insulin or both together (4, 5 and 6 cases) beside diet control.

(3) Hyperglycemic diabetic patients: 15 patients with uncontrolled DM due to unsuccessful treatment by sulfonylurea, insu-
lin or both together (6, 6 and 3 cases) beside diet control.

(4) Healthy reference group:
10 non diabetic healthy relatives of the investigated diabetic patients.

The members in the different groups were almost matched in sex, age and body weight (Table 1).

Before sampling, a frank consent was obtained directly from every patient or indirectly from a member of the patient's family after explaining the objectives of the study.

Blood sampling:
Eight ml venous blood were withdrawn from every patient in the different diabetic groups (1, 2 and 3) 3.0-4.0 hrs after the antihyperglycemic and breakfast intake as well as from the healthy reference individuals also after breakfast. From every sample 2.0 ml blood were added into an EDTA containing tube to be used for plasma glucose, creatinine and bicarbonate determinations. The remaining blood was allowed to clot at room temperature and the serum was separated by centrifugation and stored at -70°C till used for determination of the designated lysosomal enzymes within 2 months, a period that can be passed without loss of the aimed enzymes activities.
Then, hypoglycemia was promptly and adequately corrected by intravenous glucose solution administration (starting by 50% dextrose polus followed by 10% infusion). On regaining clinical (neurological) and biochemical (plasma glucose) reliable good state, further oral carbohydrate diet and sugar drinks were taken to prevent relapse before patient discharge.

Immediately before being discharged due to clinical recovery, 5 ml blood sample was withdrawn from every pre-hypoglycemic patient and serum was separated and freeze-dried till used for the designed lysosomal enzymes reassays.

**Methods:**

I. **Routine laboratory investigations for plasma glucose and creatinine determinations** (kits were obtained from Biomerieux-Vitek Inc. 595, Anglum Drive Hazelwood, Missouri 63042-2395 USA).

II. Plasma bicarbonate by AVL blood gas analyzer.

III. Assay of some acidic lysosomal enzymes:

   (1) Serum acid carbohydrazide, N-acetyl B-glucosaminidase (B-NAG), [kits are supplied from Far Sn.I. via Enrico Fermi, 1237026 Settimo di Pescantis Verona, Italy] : At pH 4.0 this enzyme catalyses the hydrolysis of p-nitro-phenil-N-acetyl B-D-glucosaminide to N-acetyl glucosamine and p-nitrophenol. The liberated p-nitrophenol is proportionate to the enzyme B-NAG activity and is determined in alkaline medium. The intensity of the yellow product together with the corresponding blank sample and blank reagent are read colorimetrically at 400-420 nm. The results are expressed in U/l (Maruhn, 1976; Gressner and Roebruck, 1982; Pokrovsky et al., 1989).

   (2) Serum acid protease, cathepsin D (CATH-D) : It is measured by incubating 0.5 ml serum for three hours with denatured bovine hemoglobin (50 mg/ml) in 0.1 M acetate buffer (pH 3.6) and the reaction is terminated by adding 0.5 M trichloracetic acid. Then, the tyrosine liberated by the protease activity is quantified by reading the blue colour produced by reaction of the serum-Hb mixture with Folin and Ciocalteu (1927) reagent in alkaline solution using a spectrophotometer at 660 nm. CATH-D activities is expressed as ug tyrosine per ml serum per hour. The standard assay was achieved by preparing solution(s) of known tyrosine content (Gove et al., 1989).

   (3) Serum nonprostatic acid phosphatase: Serum total acid phosphatase originates from both prostatic and nonprostatic (almost within the lysosomes) sources while, prostatic acid phosphatase is inhibited by L (+) tartarate, the nonprostatic tartarate labile acid phosphatase is
determined using 4-amino-antipyrine (King and Jegatheesan, 1959).

**Statistical analysis:**

All statistical calculations and graphic presentations of the data were performed by SPSS (Statistical Package for Social Science) version 11. Quantitative data were presented as mean ($X$) ± standard deviation (SD). For comparing two sets of data, Mann-Whitney $\mu$ test was used to determine the significance of the difference between two groups. The linear relation between two variables was tested by Person correlation coefficient. Less than five percent probability ($P<0.05$) was adopted as the level of statistical significance

**RESULTS**

The results of this study are shown in Tables 1-4, Figures 1-3 and Diagram 1.

**Table (1)** shows the demographic data of the studied diabetic patients (hypoglycemics, euglycemics and hyperglycemics) on different antidiabetic therapies as well as in the healthy reference group. The investigated subjects are in general matched in age, sex and body mass index (BMI in Kg/m²). However, some exceptions are found as the mean age ($p<0.05$) and BMI ($p<0.01$) in the hyperglycemic group when compared with their respective in the healthy reference group.

**Table (2)** shows the levels of plasma glucose, creatinine and bicarbonate in type 2 diabetic patients (hypoglycemics, euglycemics or hyperglycemics) versus the healthy reference group values. Plasma glucose levels (mg/dl) are significantly higher ($p<0.001$) in the hyperglycemic group and significantly lower ($p<0.001$) in the hypoglycemic group before plasma glucose correction in comparison to the corresponding values in euglycemic diabetic and reference groups. Also, plasma bicarbonate concentrations are significantly lower in the hypoglycemic patients before ($p<0.003$) but not after ($p>0.05$) regaining reliable glucose level in comparison to normal reference group data.

**Table (3)** shows the statistical data of serum lysosomal enzymes (B-NAG, CATH-D and NPAP) concentration in the studied diabetic patients (hypoglycemics, euglycemics and hyperglycemics) on different antidiabetic therapy (insulin, sulfonylurea or both together) as well as in the healthy reference group. Serum NPAP (in king-Armstrong units/dl), B-NAG (U/L) and CATH-D (ug tyrosine/ml/hr) levels increased in diabetic patients with drug induced hypoglycemia ($1.8 \pm 0.4, 10.9 \pm 3.0, 20.7 \pm 5.1$ respectively) or with uncontrolled DM and hyperglycemia ($1.1 \pm 0.3, 8.1 \pm 2.9, 17.8\pm3.7$ respectively) than those with controlled DM and euglycemia ($0.96 \pm 0.33, 5.0 \pm 1.8, 14.4 \pm 2.2$ respectively) or healthy reference ($0.8 \pm 0.25, 3.8 \pm 1.1, 13.5 \pm 1.4$ respectively) groups but no
significant difference in such lysosomal enzyme activities between the hypoglycemic diabetics before (1.8 ± 0.4, 10.9 ± 3.0, 20.7 ± 5.1 respectively) and after (1.5 ± 0.4, 9.4 ± 2.8, 16.8 ± 3.5 respectively) management and the uncontrolled hyperglycemic diabetics (1.1 ± 0.3, 8.1 ± 2.9, 17.8 ± 3.7 respectively) (Table 3). The well controlled diabetics had significantly lower mean activity of serum lysosomal enzymes than the poorly controlled diabetics.

**DISCUSSION**

Although acidic lysosomal enzymes are originally found as intracellular organelles in most tissues, small amounts of them leak to the plasma. The major factor responsible for changes in plasma levels of the acidic lysosomal hydrolases was injury of tissues rich in such enzymes. Besides their biological function within the cells, these enzymes may break down the endothelial membrane glycoconjugates. Due to variability among these enzyme bioactivities, more than one enzyme should be assayed in any protocol (Gasting et al., 2006).

In management of type 2 DM, oral antihyperglycemic should be tried before insulin therapy is allowed (Scheen, 2005). Antihyperglycemic therapy prevents or reduces morbidity and mortality caused by the relatively common serious diabetic complications (Riley and Kastrup, 2001). However, hypoglycemia may occur if more than really required antihyperglycemic therapy is taken, there is a missed meal after intake of the recommended therapy and / or development of unplanned physical or mental stress (Granner, 2000).
In the present study, accidental intake of insulin and/or oral antihyper-glycemic drug(s) in overdoses induced significant increase of the estimated serum lysosomal enzymes most probably due to the induced intracellular hypoglycemia. In this respect, the reaction to insulin was higher but shorter than sulfonylurea. At the same time, B-NAG had higher response than CATH-D and NPAP to the same antihyperglycemic drug overdoses (Table 3 and Figures 1-3). Any lysosomal enzyme may be changed independent of others reflecting the pathological rather than the pharmacological action of the inducing agent. The enhanced release of the lysosomal hydrolases may be due to increased lysosomal membrane permeability or even its degeneration. Subsequently, antihyperglycemic drug overdoses and/or the resulting induced intracellular hypoglycemia exerted a marked labilizing effect on B-NAG. The stabilizing or labilizing effect of a compound on lysosomal membrane depends highly on its dosage and exposure time (Rupar et al., 1992; Geetra, 1993). Therefore, antihyperglycemic drug(s) through their metabolic actions were involved in regulation of lysosomes biology. On the other hand, there was no significant correlation between plasma glucose concentrations and different serum lysosomal enzyme activities (Diagram 1). Discharge of patients from the hospital was encouraged only after plasma glucose levels were maintained within the reference range for at least one hour (Table 2). At this time, the determined enzymes were still significantly higher than their respective in normal controls (Table 3). This may be due to their prolonged half life simulating other plasma glycoproteins.

The results of the present study (Table 3) contradicit some experimental data. So, histochemical studies of the aortas of diabetic animals on insulin administration showed marked reduction in the activities of NPAP and B-NAG lysosomal enzymes (Wolinsky et al., 1998). In addition, Solomon and Colleagues (2000) found that insulin administration suppressed the activities of lysosomal cathepsins in rats. However, insulin injection into old animals paradoxically increased the activity of lysosomal enzymes in plasma (Gromokova and Konovalenko, 2003). Moreover in man, total NAG activities in patients with NIDDM with or without complications did not change considerably compared to the control group (Mandic and Filipovic, 1998). In turn, insulin and subsequently its secretagogues are involved in the regulation of lysosomal enzymes synthesis, secretion and/or release (Duckworth et al., 1998; Granner, 2000). The present study showed that plasma glucose levels were not correlated with serum lysosomal enzyme concentrations (Table 4). This finding confirms the belief that lysosomal enzymes production is a plasma glucose-independent process (Gromokova
In the present study (Table 3), the different serum lysosomal enzyme concentrations were significantly higher in the uncontrolled hyperglycemic patients than their corresponding values in the healthy reference group. However, they were significantly lower than their respective levels in the hypoglycemic patient group before resuscitation. Lysosomal enzymes were not completely dependent on plasma glucose level. This may be due to exhaustion of the lysosome organelles by disease chronicity. The levels of the different serum lysosomal enzymes in the controlled euglycemic patients showed no significant difference in comparison to their corresponding healthy reference group values but significantly lower than their respective in the hypoglycemic patient group.

Numerous articles have handled this subject. Diabetic patients had higher concentrations of blood lysosomal enzymes e.g., NB-acetyl glucosaminidase (B-NAG) than the control subjects (Agardh et al., 1991). Recently, it has been reported that only plasma N-acetyl-beta-D-glucosaminidase (B-NAG) but not cathepsin B activities showed higher values in type 2 diabetic patients (Piwowar et al., 2006). Moreover, type 1 diabetic patients showed significantly higher fraction B form and lower A fraction form in total B-NAG content compared with the control (Jovanovic et al., 2008). The underlying cause of the increased B-ANG plasma levels may be lysosomal fragility due to increased lipid peroxidation of the lysosomal membrane (George, 2008) inducing enzyme leakage from the damaged cells or tissues. This can explain the finding that all lysosomal enzyme activities are increased, the magnitude of which are related to the respective lysosomal enzyme content.

Further, during short-term hypoglycemic conditions (< 4.0 hour) induced by exogenous antihyperglycemic overdose, the activities of the objective lysosomal enzymes were increased (Table 3). After successful management of the hypoglycemia by parenteral glucose injection, partial but not complete correction of serum lysosomal enzyme anomalies was noted. Although hypoglycemia was corrected and clinical and routine laboratory (plasma glucose and bicarbonates) testing were regained (Table 2), serum lysosomal enzymes were still significantly higher than healthy reference and controlled diabetic groups (Table 3 and Figures 1-3).

Alternatively, the involvement of some pancreatic islet acidic lysosomal enzymes in insulin secretory process is not yet settled. In response to glucose induced insulin release, the pancreatic islet activities for N-B-acetyl- D-glucosaminidase,
cathepsin D and acid phosphatase were reduced in diabetic rats compared with the control. However, normalization of glycemia in these rats by phlorizin did not influence the lysosomal enzyme activities (Salehi et al., 1999). On the other hand, direct glucose infusion did not affect the islets activities of acid phosphatase and N-acetylbeta-D-glucosaminidase (Lundquist and Panagiotidis, 1992).

Acknowledgement:

Our sincere thanks and utmost appreciation to Dr. Ghada M.H.El-Kannishy, Assistant Professor of Internal Medicine, Faculty of Medicine, Mansoura University for her objective help and scientific advise in this article.
Table (1): Demographic data of the studied diabetic groups (hypoglycemics, euglycemics and hyperglycemics) as well as in the healthy reference group.

<table>
<thead>
<tr>
<th>Data</th>
<th>Age in Years</th>
<th>Sex</th>
<th>BMI Kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy reference group (10 cases)</td>
<td>46.9±3.5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hypoglycemic group (30 cases)</td>
<td>48.6±5.5</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Euglycemic group (15 cases)</td>
<td>48.7±4.1</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Hyperglycemic group (15 cases)</td>
<td>51.2±4.4*</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

P1 (>0.05) No significant difference between healthy vs hypoglycemic.
P2 (<0.01) Significant difference between healthy vs hyperglycemics.
P3 (<0.05) Significant difference between hypoglycemics vs hyperglycemics.
P4 (<0.05) Significant difference between hypoglycemics vs hypoglycemics.
P5 (>0.05) No significant difference between euglycemics vs euglycemics.
P6 (>0.05) No significant difference between hyperglycemics vs euglycemics.

Table (2): Plasma glucose, creatinine and bicarbonate concentration in type 2 diabetic patients (hypoglycemics, euglycemics or hyperglycemics) versus the healthy reference group values.

<table>
<thead>
<tr>
<th>Data</th>
<th>Plasma glucose mg/dl</th>
<th>Plasma creatinine mg/dl</th>
<th>Plasma bicarbonate mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy reference group (10 cases)</td>
<td>95.3±6.8</td>
<td>0.91±0.2</td>
<td>28.3±6.5</td>
</tr>
<tr>
<td>Hypoglycemic group (30 cases)</td>
<td>Before 48.1±5.1</td>
<td>0.94±0.28</td>
<td>20.1±5.8</td>
</tr>
<tr>
<td></td>
<td>After 117.3±3.9</td>
<td>0.88±0.19</td>
<td>22.4±3.3</td>
</tr>
<tr>
<td>Euglycemic group (15 cases)</td>
<td>120.8±11.7</td>
<td>1.1±0.2</td>
<td>27.0±5.0</td>
</tr>
<tr>
<td>Hyperglycemic group (15 cases)</td>
<td>279.6±23.5</td>
<td>1.3±0.27</td>
<td>26.3±6.4</td>
</tr>
<tr>
<td>P1 Significant difference between healthy vs hypoglycemic.</td>
<td>Before &lt;0.0001</td>
<td>&gt;0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>After &lt;0.0001</td>
<td>&gt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P2 Significant difference between healthy vs hyperglycemics</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>P3 Significant difference between healthy vs euglycemics</td>
<td>&lt;0.0001</td>
<td>0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>P4 Significant difference between hypoglycemics vs hyperglycemics</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P5 Significant difference between hypoglycemics vs euglycemics</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P6 Significant difference between hyperglycemics vs euglycemics</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
Table (3): Statistical data of serum lysosomal enzymes of the studied diabetic patients (hypoglycemics, euglycemics and hyperglycemics) on different antidiabetic therapy as well as in the healthy reference group.

<table>
<thead>
<tr>
<th>Data</th>
<th>Non Prostatic acid phosphatase (KAU/dl)</th>
<th>Acidic cathepsin-D (ug tyrosine/ml/hr)</th>
<th>N- B-acetyl-D glucosamindase (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy reference group (10 cases)</td>
<td>0.8±0.25</td>
<td>3.8±1.1</td>
<td>13.5±1.4</td>
</tr>
<tr>
<td>Hypoglycemic group (30 cases)</td>
<td>Before: 1.8±0.4</td>
<td>10.9±3.0</td>
<td>20.7±5.1</td>
</tr>
<tr>
<td></td>
<td>After: 1.5±0.4</td>
<td>9.4±2.8</td>
<td>16.8±3.5</td>
</tr>
<tr>
<td>Euglycemic group (15 cases)</td>
<td>0.96±0.33</td>
<td>5.0±1.8</td>
<td>14.4±2.2</td>
</tr>
<tr>
<td>Hyperglycemic group (15 cases)</td>
<td>1.1±0.30</td>
<td>8.1±2.9</td>
<td>17.8±3.7</td>
</tr>
<tr>
<td>P1 Significant different between healthy vs hypoglycemic</td>
<td>Before: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>After: &lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

P2 Significant different between healthy vs hyperglycemics: <0.0001 <0.0001 <0.0001

P3 Significant different between healthy vs euglycemics: >0.05 <0.05 >0.05

P4 Significant different between hypoglycemics vs hyperglycemics: <0.0001 <0.0001 <0.01

P5 Significant different between hypoglycemics vs euglycemics: <0.0001 <0.0001 <0.0001

P6 Significant different between hyperglycemics vs euglycemics: >0.05 <0.05 <0.0001

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Figure (1): Serum NPAP concentration in patients with accidentally antidiabetic drug induced hypoglycemia before and after its correction.
Figure (2): Serum B-NAG concentration in patients with accidentally antidiabetic drug induced hypoglycemia before and after its correction.

Figure (3): Serum CATH-D concentration in patients with accidentally antidiabetic drug induced hypoglycemia before and after correction.
### Diagram (1): Positive correlation between different variables in healthy reference, (1) hypoglycemic (2), euglycemics (3) and hyperglycemic (4) diabetic patients.

N: Non-significant (P>0.5) difference.
S: Significant (P<0.05) difference.
REFERENCES


تأثير الجرعات المفرطة العرضية لإمدادات ارتفاع مستوى الجلوکوز بالدم على معدات بعض إنزيمات الأجسام المجلدة (الليسوبرومات) بمصل الدم في مرضى البول السكري من النوع الثاني

المشتركون في البحث

د. شريف محمد حسن القياسي

د. عزة عبدالباقي البيومي

د. إبراهيم أحمد عبد العال

د. هبة جمال قطب

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كلية الطب - جامعة النصرة، الطب المخبر والسموم الإكلينيكية - كلية الطب - جامعة القاهرة

الأجسام المجلدة أي الليسوبرومات عبارة عن طرف مداخلها إنزيمات حمضية النشاط وهي موجودة في سيتروبلازم الخلايا. وعادة ما تستجيب هذه الإنزيمات إلى بلازما الدم عند ضرب هذه الإنزيمات من الأجسام المجلدة داخل الخلوية ومع أن طبيعة نشاط إنزيمات الليسوبرومات الحرة بالدم غير محددة على الرئة الأعضية إلا أنها تلتقي مع ضرب على الوضع الفيسيولوجي لأجسام المجلدة داخل الخلايا.

إن مرض السكر البولي هو من الأمراض المؤثرة على بعض الخلايا وبالتالي على الليسوبرومات بها ويتجلى تعبير عن إنزيمات المجلدة بزيادة

جرعات الأنسولين أو السلفونيل بوريا أو كليهما معاً موضوعاً يستحق الدراسة.

من هذا البحث دراسة تأثير معدلات نشاط بعض الإنزيمات المجلدة بمصل الدم في مرضى البول السكري المصابين ببهدوء حاد في معدل الجلوکوز بالدم نتيجة تعبير جرعات زائدة على مدة من الأنسولين أو السلفونيل بوريا.

تمت هذه الدراسة على 30 مريضاً يعانون من مرض البول السكري من تطورها بالصدفة جرعات زائدة على مدة من الأنسولين الدم أو أحد مستخلل السلفونيل بوريا أو كليهما مع ثبت فيه مستوي السكر بالدم عن المعدل الطبيعي وردت أعراض الإكلينيكية، تم إجراء الفحوصات الوراثية المختلفة ل hồلة المرض إلى جانب الدراسات الخاصة بإمدادات الليسوبرومات بمصل الدم وآمل أنها: كايسس د - بيتا إن استيل جلوکوز أمينيداز و إنزيم الفوسفاتاز الحمض.

لقد أوضح هذه الدراسة أن تعبير الأنسولين أو مرکبات السلفونيل بوريا عرضية بجرعات أكثر مما هو مقدر علرياً لمرض السكر البولي قد تسبب في زيادة معدلات إنزيمات الليسوبرومية بمصل الدم وقد كان تأثير تعبير الأنسولين أقوى ولكن لمدة أقصر من تأثير السلفونيل بوريا، وفي المقابل كان إنزيم بيتا جلوکوز أمينيداز أكثير تأثراً بينما كان إنزيم الفوسفاتاز الحمض لا تأثراً بعد تعبير الأنسولين أو السلفونيل بوريا بمكبات زائدة.

الخلاصة: إن معدلات نشاط بعض إنزيمات الأجسام المجلدة الليسوبرومات بمصل الدم في مرضى البول السكري قد زادت عن مستوياتها في المجموعة الضابطة من الأصداء نتيجة تعبير جرعة زائدة من الأنسولين أو السلفونيل بوريا أو كليهما بمعالجات مختلفة. وقد استمر هذا الخلط لفترة ما بتصفح معدل الجلوکوز بالدم.
