COMPARISON OF SERUM ADIPONECTIN AND INTERLEUKIN 6 CONCENTRATIONS IN NONDIABETIC HYPERTENSIVE AND DIABETIC HYPERTENSIVE PATIENTS WHO DEVELOPED CEREBRAL INFARCT

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ABSTRACT:
Stroke is the second leading cause of death and a major cause of morbidity and mortality in western as well as developing countries. Adiponectin is a fat-derived plasma protein that has beneficial actions on cerebrovascular disorders. A low level of plasma adiponectin is associated with increased mortality after ischemic stroke. Interleukin 6 is a cytokine, which is elevated in inflammatory, traumatic and ischemic injuries. The objective of this study was to compare serum adiponectin and interleukin-6 levels in diabetic hypertensive and nondiabetic hypertensive patients and to measure the size of cerebral infarct. 89 patients (30 controls, 30 nondiabetic hypertensive and 29 diabetic hypertensive) were recruited in the study according to inclusion criteria of Ziauddin University Hospital. Serum adiponectin and interleukin 6 concentrations were measured by ELISA. Blood glucose and lipid profile was done by standard kit methods. Serum adiponectin concentration was significantly lower (P<0.05) in both study groups and interleukin 6 concentration was significantly higher (P<0.05) in diabetic hypertensive group as compared with controls. The mean serum interleukin 6 in diabetic hypertensive patients with cerebral infarct was significantly higher than that of nondiabetic hypertensive patients with cerebral infarct (P < 0.001). Serum adiponectin concentration was decreased while the infarct size was larger in diabetic hypertensive group as compared to nondiabetic hypertensive group but the difference in these parameters was statistically non significant. Hence the study supports to the evidence of involvement of adiponectin and interleukin 6 in patients of stroke.

Keywords: Stroke, Morbidity, Adiponectin, Interleukin 6, Infarct.

INTRODUCTION

Stroke is defined as rapidly developing symptoms and/or signs of focal and at times global loss of cerebral functions lasting for 24 hours or more with no apparent cause of other than that of vascular origin (Park and Park, 1995). Stroke is a major cause of death and disability in Western countries (Rosamond et al., 2007).

Hypertension and type 2 diabetes mellitus are very frequently seen in all medical settings and are considered to be important risk factors for stroke (Goldstein et al., 2006). One study, which was conducted at Abbottabad reported 56.04% incidence of hypertension in stroke patients (Khan et al., 2006). Diabetes mellitus not significantly increases the risk of stroke, but also a predictor of reduced survival following stroke (Jorgensen et al., 1994; Laing et al., 2003; Oliveira et al., 1988). It has become an established fact that inflammation plays an important role in cerebrovascular diseases.

Adiponectin, an adipose tissue-specific plasma protein plays a vital role in regulating

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energy homeostasis, glucose and lipid metabolism and inflammatory responses in vascular system (Diez and Iglesias, 2003; Goldstein and Scalia, 2004; Ouchi et al., 2003). Literature survey provides an evidence that hypo adiponectinemia has been associated with type 2 diabetes mellitus and stroke (Iwashima et al., 2004; Chen et al., 2005). Data from human and animal studies suggest that this adipocytokine has insulin sensitizing, antiatherogenic and anti-inflammatory properties (Chamorro, 2004). One of the potential mechanism(s) of adiponectin action includes inhibition of smooth muscle proliferation, monocyte adhesion to endothelium and macrophage uptake by low density lipoproteins (Chen et al., 2005).

Human interleukin 6 is a single polypeptide chain of 185 amino acids that is encoded by the IL6 gene (Ferguson et al., 1998). It is primarily secreted by adipose tissues and skeletal muscles and has many metabolic and endocrine functions (Dimitris et al., 1998). Studies have demonstrated high level of serum interleukin 6 in stress, (Fassbender et al., 1994) traumatic and other diseases including stroke (Acalovschi et al., 2003; Davalos et al., 1997). Limited studies have been carried out to determine serum adiponectin and serum interleukin 6 level in nondiabetic hypertensive and diabetic hypertensive patients and their association with cerebral infarct size.

Objective of the Study

To compare serum adiponectin and serum interleukin 6 concentrations in nondiabetic hypertensive and diabetic hypertensive patients who developed cerebral infarct and their association with cerebral infarct size.

MATERIAL AND METHODS

The study included 89 subjects between the age group of 50 to 70 years, who were selected from Ziauddin and Liaquat National Hospitals, Karachi. Informed consent was obtained from all subjects themselves or by relatives as legally required prior to participation in the study following approval of the study by the ethical committee of Ziauddin University. Convenient sampling was done to recruit the subjects.

Patients with major cardiac, renal, hepatic and cancerous diseases, stroke due to aneurismal rupture, arteriovenous malformations recent (within one month) history of head trauma, transient ischemic attack, intracerebral hemorrhage, CT/MRI results that were inconclusive for the lesion location, coronary artery disease or collagen disease were excluded from the study. Women on hormone replacement therapy, smokers and/or alcohol consumers were also excluded from the study.

89 subjects were divided into three groups. Control group comprises of 30 subjects who were matched for age, sex and BMI with study groups. First study group comprised of 30 nondiabetic hypertensive patients who developed stroke and second group comprised of 29 diabetic hypertensive patients who developed stroke.

Study Protocol

Fasting plasma samples were obtained and stored at -80°C for subsequent assay within 48 hours of stroke onset. The serum adiponectin (Suominen, 2004) and interleukin 6 (Nishimoto et al., 2000) concentrations were determined by chemiluminescent enzyme immunoassay (CLETIA) (Fujireb ionic, Tokyo, Japan). Fasting and random blood glucose was done by glucose oxidase method using kit obtained from Merck (Trinder, 1969). Triglyceride (Bucolo et al., 1973), cholesterol, LDL cholesterol and HDL cholesterol (Allian et al., 1974) were also done by kits obtained from Merck.

STATISTICAL ANALYSIS

Data of all quantitative variables was shown as mean and standard error of mean. Analysis was performed using the statistical package for social sciences (SPSS version 12). P value was determined by t test and the value <0.05 was considered statistically significant.
RESULTS

The study comprised of 89 patients. 30 of them were control while 59 (30 nondiabetic hypertensive and 29 diabetic hypertensive) were cases who developed cerebral infarct. Serum adiponectin and interleukin 6 concentrations were compared among these groups. Serum adiponectin concentration was significantly lower (P<0.05) in nondiabetic hypertensive patients with cerebral infarct and diabetic hypertensive patients with cerebral infarct while the interleukin 6 concentration was significantly higher (P<0.05) in diabetic hypertensive group with cerebral infarct as compared with controls that is shown in table1. Table 2 showed that among the two study groups, mean serum interleukin 6 concentration in diabetic hypertensive patients with cerebral infarct was significantly higher than that of nondiabetic hypertensive patients with cerebral infarct (26.44 ± 0.94 versus 21.57 ± 0.85; P<0.001). Of the 59 study subjects with and without diabetes, no statistically significant difference was found in infarct size.

Serum adiponectin concentration was decreased while the infarct size was larger in diabetic hypertensive group as compared to nondiabetic hypertensive group but the difference in these parameters was statistically non significant. Hence the study supports to the evidence of involvement of adiponectin and interleukin 6 in patients of stroke.

DISCUSSION

In our study we focus the serum adiponectin and interleukin 6 concentrations in nondiabetic hypertensive and diabetic hypertensive patients. Ischemic stroke occurs with many obesity-related disorders that are associated with hypoadiponectinemia (Goldstein et al., 2006; Ouchi et al., 2003). It is documented by Masakim et al in 2008 that adipose-derived hormone adiponectin protects the brain from ischemic injury (Nishimura et al., 2008) while high level of serum interleukin 6 is associated with stroke (Acalovschi et al., 2003).

Epidemiological studies have shown that hypoadiponectinemia could be a useful biomarker for the presence of ischemic stroke and increased mortality after ischemic stroke (Efstathiou et al., 2005; Chen et al., 2005). In our previous study (Aqil et al., 2008), we have already stated that serum adiponectin level was significantly lower in ischemic stroke patients as compared to the normal age, sex and BMI matched healthy individuals. This current study also supported the evidence of hypoadiponectinemia in patients with cerebral infarct that was either developed in nondiabetic hypertensive or diabetic hypertensive group. Although the difference of serum adiponectin concentration is not statistically significant between our study groups but in the light of present observations and literature survey it may be concluded that adiponectin acts as an endogenous modulator of brain injury in response to acute ischemia and hypoadiponectinemia participates in the exacerbated ischemic stroke. Recently, a clinical study has suggested an association between hypoadiponectinemia and increased mortality after ischemic stroke and a negative correlation between adiponectin concentration and initial infarct volume (Efstathiou et al., 2005). This association was supported by our study as well but no statistically significant difference was observed in cerebral infarct volume between both study groups and this non significant statistical figure in this parameter might be due to the small number of patients in each group.

In our study interleukin 6 concentration was significantly higher only in diabetic hypertensive group as compared to nondiabetic hypertensive and control groups, suggesting that probably interleukin 6 has some association with the diabetes mellitus and not directly with the occurrence of cerebral infarct. Basically interleukin 6 acts as both a pro-inflammatory and anti-inflammatory cytokine and is one of the most important mediators of acute phase response (Van et al., 1997). Literature survey stated that induction of interleukin 6 is a common feature of various acute brain diseases including
Comparison of serum adiponectin and interleukin 6 concentrations in control and study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls Mean ± SEM (n=30)</th>
<th>Nondiabetic hypertensive Mean ± SEM (n=30)</th>
<th>Diabetic hypertensive Mean ± SEM (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum adiponectin (ng/dL)</td>
<td>12.46 ± 0.56</td>
<td>7.66 ± 0.46*</td>
<td>6.84 ± 0.34*</td>
</tr>
<tr>
<td>Serum interleukin 6 (pg/mL)</td>
<td>22.76 ± 0.76</td>
<td>21.57 ± 0.85</td>
<td>26.44 ± 0.94*</td>
</tr>
</tbody>
</table>

* Statistically significant as compared with controls.

Table 2
Plasma adiponectin, interleukin 6 and blood lipid levels in nondiabetic hypertensive and diabetic hypertensive patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nondiabetic hypertensive Mean ± SEM (n=30)</th>
<th>Diabetic hypertensive Mean ± SEM (n=29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.99 ± 0.13</td>
<td>1.765 ± 0.06</td>
<td>0.132</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.93 ± 0.23</td>
<td>4.75 ± 0.15</td>
<td>0.540</td>
</tr>
<tr>
<td>LDL-Cholesterol (mmol/L)</td>
<td>3.17 ± 0.18</td>
<td>2.89 ± 0.16</td>
<td>0.263</td>
</tr>
<tr>
<td>HDL-Cholesterol (mmol/L)</td>
<td>1.15 ± 0.06</td>
<td>1.27 ± 0.07</td>
<td>0.206</td>
</tr>
<tr>
<td>Serum adiponectin (ng/dL)</td>
<td>7.66 ± 0.46</td>
<td>6.84 ± 0.34</td>
<td>0.171</td>
</tr>
<tr>
<td>Serum interleukin 6 (pg/mL)</td>
<td>21.57 ± 0.85</td>
<td>26.44 ± 0.94</td>
<td>0.000</td>
</tr>
<tr>
<td>Infarct size (mm)</td>
<td>14.43 ± 1.12</td>
<td>17.31 ± 1.19</td>
<td>0.085</td>
</tr>
</tbody>
</table>

cerebral ischemia (Juttler et al., 2002). Many studies also suggested that interleukin 6 is upregulated within few hours of cerebral ischemia (Loddick et al., 1998; Suzuki et al., 1999) and this finding is consistent with one of the part of our study as well, which was observed in diabetic hypertensive patients. Hypoadiponectinemia may directly or indirectly be involved in development of cerebral infarct and high serum concentration of interleukin 6 seemed to be associated with diabetic hypertensive patients.

CONCLUSION

In the light of present investigations it is stated that plasma interleukin 6 might not be directly associated with the development of cerebral infarct while low concentration of plasma adiponectin may be considered as a risk factor for the development of cerebral infarct. Hence adiponectin qualifies for further research to confirm this hypothesis and to explore molecular mechanism(s) behind it.

REFERENCES


