Effects of insulin and sulphonylureas on insulin-like growth factor-I levels in streptozotocin-induced diabetic rats

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Submitted: August 6, 2002
Accepted: October 30, 2002

Key words: IGF-I; diabetes; insulin; sulphonylurea

Abstract

OBJECTIVE: Diabetes Mellitus is associated with decreased insulin-like growth factor-I (IGF-I) levels and also, poor growth in diabetes is related with low circulating levels of IGF-I. Insulin acts via an increase of IGF-I synthesis on growth. We studied the effects of insulin and sulphonylureas on serum IGF-I levels and aimed to evaluate the restoration of IGF-I in different therapeutic strategies.

DESIGN AND SETTING: Thirty male rats were used in the study and diabetes was induced by a single intraperitoneal injection of streptozotocin (35 mg/kg body weight). After confirmation of hyperglycemia, rats were divided into three groups. The first group was treated with insulin, and second group with glimepiride, third group was not treated (control group). IGF-I levels were measured at basal, after streptozotocin and at the end of the treatment period.

RESULTS: Serum IGF-I levels were found to decrease from 577.2 ng/ml to 253.0 ng/ml after streptozotocin (p<0.005). After 1 month, IGF-I levels were found 524.0 ng/ml in insulin group, 449.3 ng/ml in sulphonylurea group, and 313.1 ng/ml in control group. The increase in IGF-I was statistically significant in insulin group (p<0.005), and in sulphonylurea group (p<0.05), but it was not significant in control group (p>0.05).

CONCLUSIONS: Serum IGF-I levels decrease in diabetes and insulin treatment restores IGF-I depletion significantly. And although less effective, treatment with glimepiride restores IGF-I levels significantly.

Introduction

Diabetes Mellitus is associated with decreased insulin-like growth factor-I (IGF-I) levels [1,2] and poor growth in diabetes is related with low circulating levels of IGF-I [3]. Also multiple factors contribute to the growth retardation which is a characteristic feature of uncontrolled diabetes, diminished IGF-I expression and inhibition of available IGF-I may explain the impaired growth in diabetics [4].

Studies in diabetic rodents and humans provide evidence that IGF-I may alleviate the diabetic state and insulin resistance to some degree [5]. More recent studies focused on the role of IGF-I
deficiency as a contributing factor to the metabolic dys-
function in patients with diabetes [6]. Recombinant
human insulin-like growth factor-I (rhIGF-I) was found
to improve glycemic control and enhance insulin sensi-
tivity in patients with severe insulin resistance [7–9].
IGF-I has good metabolic effects on glucose uptake
and production in diabetic rats in which insulin-stimu-
lated glucose uptake was impaired [10]. Further, IGF-I
potently inhibits the secretion of insulin from pancre-
atic beta-cells, which appear to possess IGF-I but not
insulin receptors [11–13].

It was shown that growth arrest in the diabetic rats
was corrected by insulin infusion which also restored
growth hormone secretion [14–16]. Insulin-deficient
growth-arrested diabetic animals have reduced serum
IGF-I levels which are restored towards normal by
insulin but not by growth-hormone treatment. Normal
growth of diabetic rat is restored by infusion of recom-
binant human IGF-I without normalization of the blood
sugar level and that insulin acts via an increase of
IGF-I synthesis on growth of diabetic rats [17]. But,
there is no sufficient data about the effects of sulpho-
nylureas on IGF-I levels in diabetics. In a study, Heinze
et al found that glibenclamide promotes the growth of
human chondrocytes in culture and concluded that this
effect is mediated by IGF-I dependent mechanisms [18].
We studied the effects of insulin and sulphnylureas on
serum IGF-I levels and aimed to evaluate the restora-
tion of IGF-I in different therapeutic strategies.

Materials and Methods

Induction of diabetes. Male Spraque-Dawley rats
weighing 180–220 gram were used in the study. Diabe-
tes was induced in 12 to 18-hour fasted rats by a single
intraperitoneal injection of streptozotocin (35 mg/kg
body weight). 72–96 hour after the injection, hypergly-
cemia was confirmed by measuring blood glucose level-
s using a glucometer (One Touch Profile, Lifescan).
Thirty rats that had became diabetic were used in the
study.

Study groups. Once hyperglycemia confirmed, rats
were divided into three groups that contains 10 rats
in each group. The first group was treated with insu-
lin (Novo Nordisk) – insulin group –, and second group
with glimepiride (Aventis) – sulphnylurea group –
by measuring blood glucose levels using a glucometer
that allowed glycaemia to be maintained in the required
range. Third group was not treated (control group).

Serum IGF-1 measurements. Serum IGF-1 levels
were measured by radioimmunoassay method with
DSL-2900 Rat IGF-1 RIA Kit (Diagnostic System Labo-
ratories, Inc). IGF-1 measurements of rats were per-
formed three times. First, at the beginning of the study;
second two weeks after rats became diabetic; and third,
at the end of the study, after different therapeutic regi-
mens were applied to the rats for one month.

Statistical analysis. Data (expressed as the mean
± SEM) were compared using the two-tailed Student’s
t test and Mann-Whitney U test for paired data, p <
0.05 was considered statistically significant. Analysis
program was SPSS 10.0 for Windows.

The study has been approved by the “Animal Care
Ethics Committee” of Ege University Faculty of Medi-
cine.

Results

Serum IGF-1 levels of 30 rats that were included
into the study decreased from 577.26 ±96.03 ng/ml
to 253.08 ±109.99 ng/ml after induction of diabetes
with streptozotocin (Table 1). The decrease of serum
IGF-1 levels is statistically significant (p<0.005). After
1 month of treatment period, IGF-1 levels were found
524.08 ±68.31 ng/ml in insulin group, 449.30 ±148.01
ng/ml in sulphonylurea group, and 313.14 ±90.85 ng/ml
in control group. The increase in IGF-I was statistically
significant in insulin group (p<0.005), and also in sul-
phonylurea group (p<0.05), but it was not significant
in control group (p>0.05). Serum IGF-I levels of rats in
each of the groups after induction of diabetes and after
treatment period with insulin or sulphonylurea (or not
treated) are shown in table 2.

Discussion

Diabetes is associated with a fall in serum levels of
insulin-like growth factor-I and a rise in somatomedin
inhibitor, a factor which antagonizes somatomedin ac-
tion [19]. Studies demonstrated that total IGF-I levels
are reduced in the face of elevated plasma growth hor-
mone levels in patients with poorly controlled diabetes
[20–22]. Poor growth in diabetes involves low circulat-
ing levels of insulin-like growth factors, largely reflect-
ing decreased growth factor release by the liver [3].
IGF-I can restore growth in diabetic rats. Both insulin
and IGF-I treatment increase the growth rate of dia-
betic rats to near normal when infused at sufficiently
high doses. However, at equivalent growth rates, IGF

treatment leads to a greater rate of protein deposition
[23]. Also, diabetes mellitus is associated with decreased
levels of circulating insulin-like growth factor binding
protein-3 (IGFBP-3), which are restored toward normal
by treatment with insulin and/or infusion of IGF-I [24].

It was found that one week after administration of
streptozotocin, IGF-I concentrations significantly de-
creased and no further decrease was observed after 1
month of diabetes [15]. We measured serum IGF-I lev-
els two week after streptozotocin and found significant
decrease in IGF-I levels when the rats became diabetic.
After treatment period, serum IGF-I levels were in-
creased in the groups treated with insulin (p<0.005)
and sulphnylureas (p<0.05) significantly on the con-
trary to that of the control group (p>0.05). The signifi-
cant increase in IGF-I levels with insulin is well-adjusted
with the literature. In a study, the streptozotocin-
treated rats were found to have a 39% reduction in the
serum level of insulin-like growth factor-I compared to
control rats (0.33 ±0.02 mg/ml and 0.54 ± 0.02 mg/ml
respectively) and insulin treatment during the regen-
eration period completely restored the IGF-I level back
to normal [25]. But, there is no data about the effects
of sulphnylureas on IGF-I levels in diabetics. It was
shown that insulin and IGF-I binding to neuroblastoma
cells was increased by 13% and 7% respectively follow-
ing a 24 hour incubation with the sulphonylurea glyburide [26]. Sulphonylureas can show similar effects of insulin because of the stimulation of insulin secretion in subjects that have insulin reserve. In our study, 35 mg/kg streptozotocin was applied to rats and they were became mild diabetic, so we thought that insulin reserve was kept partially. It was shown that with a single injection of low dosage streptozotocin (35 mg/kg), a rat model of moderate diabetes originating from a partial loss of pancreatic beta-cells can be obtained that characterized by slight basal hyperglycemia and hypoinsulinemia, but also by severe glucose intolerance and impaired in vivo and in vitro insulin secretion in response to glucose [27].

In conclusion, serum IGF-I levels decrease in diabetes and insulin treatment restores IGF-I depletion significantly. Although less effective, treatment with glibenpiride also restores IGF-I levels significantly. So, the study suggested that poor growth in uncontrolled diabetic can be restored with insulin and also with sulphonylureas. But, further studies are needed to evaluate the effects of insulin and especially sulphonylureas on IGF-I levels in diabetics.

REFERENCES


