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Short communication

Associations of blood levels of insulin-like growth factor (IGF)-I, IGF-II and IGF binding protein (IGFBP)-3 in schizophrenic Arab subjects

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Abstract

Background: Insulin-like growth factors (IGFs) are believed to be important in brain development and repair following neuronal damage. It is also speculated that IGFs are involved in the association of foetal and pre-adult growth with schizophrenia (SZ).
Methods: The aim of this study was to assess levels of IGF-I, IGF-II and IGF binding protein (IGFBP)-3 and their associations in male Arab patients with SZ (n=53) and healthy control subjects (HC; n=52). Anthropometric and demographic data were collected for each subject for whom blood specimens were analysed for serum lipoproteins, apolipoprotein B (apoB), IGF-I, IGF-II and IGFBP-3.
Results: The SZ group had lower serum total cholesterol, apoB and uric acid levels than the HC group ($p<0.05$). IGF-II levels were significantly higher in the SZ group ($p=0.02$) and correlated positively with levels of atherogenic lipoproteins – total cholesterol, low-density lipoprotein, apoB – and IGFBP-3. The pattern of correlations between the IGFs and the various parameters differed somewhat between the HC and SZ groups.
Conclusions: These results demonstrate that IGF-II levels are increased in patients with SZ and show significant associations with atherogenic lipoproteins. We suggest a possible link between IGF-II metabolism and atherogenesis in SZ.
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Keywords: Arabs; atherogenic dyslipidaemia; insulin-like growth factor-I (IGF-I); IGF-II; insulin-like growth factor-binding protein (IGFBP); schizophrenia.

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The prevalence of schizophrenia (SZ) is increasing worldwide, but its aetiopathogenesis essentially remains poorly characterised. Recently, pathogenetic links with altered insulin-like growth factor (IGF) metabolism and binding have been suggested. IGF-I and IGF-II and their binding proteins (IGFBP-1–6) are physiologically important in post-natal and pubertal development, as well as in adult life (1, 2). It has recently been speculated that environmental exposure influences the risk of SZ through mechanisms mediated by changes in IGF-I and IGF-II (3, 4). Indeed, IGF-I plays an important function in early neural development and neuroprotection following head injury (5), possibly by exerting powerful anti-apoptotic effects (6). This study explored these various hypotheses further by comparing blood levels of IGF-1, IGF-II and IGFBP-3 between stable SZ patients and healthy control (HC) subjects, and assessing biochemical, demographic and anthropometric determinants of circulating IGF levels in both groups.

Two age- and body mass index (BMI)-matched groups of male subjects were enrolled in the study after providing informed voluntary consent, as follows: (a) 52 apparently HC subjects recruited from those presenting at the Central Blood Bank, Kuwait for regular blood donation from across the whole city state; and (b) 53 SZ patients with proven chronic SZ diagnosed according to the ICD-10, DSM-IV criteria (7–9) and considered stable on anti-psychotic medication (essentially haloperidol at variable doses up to 30 mg/day coupled with anti-cholinergic/anti-parkinsonism drugs: benztropine 2–6 mg/day or benzhexol 5–15 mg/day). The SZ group was diagnosed as schizophrenic and had been followed up for at least 1 year after initial presentation at the Psychiatric Hospital, Kuwait. Consent was obtained from patients' relatives in all cases and in the presence of each patient's social welfare officer. We obtained ethical approval for the study from our Institutional Research Ethics Committee.

None of the subjects in either group smoked on a regular basis or had any associated comorbidity (such as epilepsy, substance abuse, organic brain syndrome, chronic infections, chronic systemic illness, especially diabetes and hypertension and coronary heart disease) or were or had been on any form of hypoglycaemic or hypolipidaemic medication. Social classification in Kuwait is essentially homogeneous with a cradle-to-grave welfare system; therefore, the HC and SZ groups were similar in socioeconomic status.

Anthropometric measurements (height, weight and waist and hip circumferences) were taken for each subject, and BMI and waist-to-hip ratio (WHR) were calculated. Blood samples were obtained from each subject, from which serum was extracted for glucose, uric acid and lipids [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and direct low-density lipoprotein cholesterol (LDL-C)] analyses using a Beckman-Coulter LX-20 autoanalyzer (Beckman Coulter Inc., Fullerton, CA, USA). Serum levels of apolipoprotein B (apoB) were determined by nephelometry using a Beckman IMMAGE® analyzer (Beckman Coulter Inc., Fullerton, CA, USA). IGF-I, IGF-II and IGFBP-3 assays were performed using an ELISA kit (DSL, Webster, TX, USA) on batched specimens that were stored frozen without any prior thawing at −70°C, and for no longer than 3 months. The intra- and inter-assay coefficients of variation for IGF-I, IGF-II and IGFBP-3 assays were always <5.0%. Values are expressed as median (range). Differences between the two groups (HC and SZ) were analysed using the Mann-Whitney U-test. Correlations between IGF-I, IGF-II and IGFBP-3 and the other measured parameters were determined using Spearman's rank correlation coefficients (r_s). These tests were performed using SPSS software (SPSS 14.0 for Windows, SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

The demographic, anthropometric and biochemical parameters including IGF-I, IGF-II and IGFBP-3 levels in the SZ and HC groups are shown in Table 1. Both groups were matched for age, BMI and WHR. However, the SZ group had lower TC, apoB and uric acid levels than the HC group. While IGF-I and IGFBP-3 levels were similar for both groups, the SZ group had significantly higher IGF-II levels ($p=0.02$). When the SZ and HC groups were subdivided according to BMI as normal weight (≤ 25 kg/m^2) and overweight (>25 kg/m^2), and the various parameters were compared between the two weight subgroups for either group, there were no significant differences in values for any parameter. Correlative analyses for the SZ group showed that IGF-I did not correlate significantly with any of the measured parameters, while IGF-II had highly significant ($p<0.01$) correlations with TC ($r_s=0.36$), LDL ($r_s=0.41$) and IGFBP-3 ($r_s=0.82$). None of the growth factors correlated significantly with BMI, WHR and age. The findings in relation to IGF-II and atherogenic lipids persisted on multiple regression analysis after correcting for IGFBP-3 levels.

These results suggest that the SZ patients have a less atherogenic profile (lower TC, uric acid and apoB levels) than an age- and BMI-matched control group. Interestingly, IGF-II is the only growth factor that differed in levels between the HC and SZ groups, and correlative analysis showed significant linear relationships with the atherogenic lipids that persisted even after controlling for IGFBP-3 levels. There were no relationships with age and BMI, and the associations persisted in SZ patients independent of type of antipsychotic medication. This is of some interest, especially as, unlike IGF-I, the biology of IGF-II is essentially still unclear. In the adult human and higher mammals, IGF-II concentrations remain persistently high (more than four-fold higher than levels of IGF-I, as also observed here), unlike in rodents, in which IGF-II is undetectable in adult circulation (1, 2). IGF-II is ordinarily important in utero, where it is involved in placental function and nutrient partitioning under the regulation of genes that are imprinted (10). Studies using gene knock-out models (11, 12) have indeed suggested that IGF-II can bind to IGF-I receptors in conditions in which the IGF-II receptor has been inactivated, particularly during natal development. Since SZ may have foetal origins, it is therefore tempting to speculate that IGF-II plays a major role in its genesis, also probably through links with the atherogenic lipids. This notion merits further study with greater subject numbers.

We studied a relatively homogeneous group of non-smokers who were neither diabetic nor hypertensive, as these disorders and/or their treatment can affect growth factor levels. Similarly, we studied only male subjects, as it has been reported that cyclical

Table 1 Demographic, anthropometric and biochemical parameters including IGF-I, IGF-II and IGFBP-3 levels in schizophrenic patients and healthy control subjects.

Variable	Schizophrenic patients	Healthy controls	p*
N	53	52	–
Age, years	40.5 (22.0–69.0)	41.0 (27.0–60.0)	0.35
BMI, kg/m^2	28.3 (17.8–51.6)	29.8 (19.8–38.6)	0.16
WHR	0.91 (0.85–1.10)	0.93 (0.87–1.08)	0.12
TC, mmol/L	4.13 (2.61–7.17)	4.68 (2.39–6.35)	0.05
HDL, mmol/L	0.79 (0.49–1.15)	0.85 (0.52–1.17)	0.15
LDL, mmol/L	2.69 (1.14–5.31)	2.78 (1.09–4.59)	0.60
apoB, g/L	0.86 (0.54–1.86)	1.04 (0.62–1.51)	0.03
Uric acid, μmol/L	269 (61–455)	323 (165–412)	<0.01
IGF-I, nmol/L[a]	23.2 (6.1–66.2)	19.8 (10.4–60.5)	0.15
IGF-II, nmol/L[a]	187.9 (107.4–317.8)	159.7 (103.6–347.2)	0.02
IGFBP-3, nmol/L[b]	185.5 (85.3–311.5)	180.5 (106.7–340.2)	0.21

Values are expressed as median (range). n, number of subjects; BMI, body mass index; WHR, waist-to-hip ratio; TC, total cholesterol; HDL, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol; apoB, apolipoprotein B; IGF-I, insulin-like growth factor-I; IGF-II, insulin-like growth factor-II; IGFBP, insulin-like growth factor binding protein; [a]IGF-I and IGF-II, conversion factor between ng/mL and nmol/L: ng/mL×0.13=nmol/L. [b]IGFBP-3, conversion factor between ng/mL and nmol/L: ng/mL×0.035=nmol/L. *p for differences between the two groups of subjects.

hormonal changes in women can affect growth factor levels (13), although we did not specifically measure testosterone levels in our patients. As a result, these exclusion factors reduced our subject numbers. An important limitation of the study is its cross-sectional, case-control design, an approach used because of the nature of the SZ patients, for whom long-term follow-up in the Arab cultural setting is often a major social problem and for whom, for ethical considerations, treatment cannot be withdrawn for experimental purposes for florid cases. Nonetheless, this study is important as probably the first such study in an Arab population to specifically explore the putative links between IGF pathophysiology and SZ.

We conclude that IGF-II levels are increased in SZ patients and positively correlated with levels of atherogenic lipoproteins. We suggest a link between IGF-II metabolism and atherogenesis in SZ that should be explored in further studies.

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