ORIGINAL ARTICLE

Prevalence of Insulin Resistance in Schizophrenia in HUKM

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SUMMARY

This is a cross-sectional study to determine the prevalence of insulin resistance and its associated factors in Hospital UKM patients with schizophrenia using the Homeostatic Model Assessment (HOMA) model. Fasting glucose and insulin from 85 patients were obtained. Fasting glucose revealed 15% of the patients were diabetic, while another 15% had impaired fasting glucose. Using the HOMA model, 68% of the patients had insulin resistance. Univariate analyses found BMI (p<0.001) and waist circumference (p<0.001) to be associated with insulin resistance. The statistical significance disappeared after multivariate analyses. All patients with schizophrenia should be screened and managed as a group at high risk for development of diabetes with emphasis on body weight management.

KEY WORDS:
Diabetes, Schizophrenia, Insulin resistance, Homeostatic Model Assessment, Body weight, Waist circumference

INTRODUCTION

Type 2 diabetes mellitus appears to be more common in schizophrenia, with studies demonstrating prevalence rates to be 15-18%. This approximates to two to four times the general population rate[1, 2, 3]. The observation that some patients were not on antipsychotic medication when they developed type 2 diabetes mellitus[3] suggests that the disorder itself renders patients vulnerable to developing glucoregulatory abnormalities. This area has in recent years become a concern due to the observed association of hyperglycaemia with not only conventional antispychotics but particularly more so with the now widely-used atypical antipsychotics [2, 4].

Insulin resistance occurs when normal insulin concentrations fail to produce a normal biological response and precedes development of diabetes. Possibly up to 20-40% of the adult population have insulin resistance although a quarter of these people have normal glucose levels[5,6]. One method of measuring insulin resistance is using the Homeostatic Model Assessment (HOMA)[7], which is a mathematical feedback model to yield an estimate of insulin resistance from fasting plasma glucose and insulin. It is easy to do, has been validated against a variety of physiological methods and widely used [8]. Knowledge about the prevalence of insulin resistance and its influencing factors in schizophrenia would help us take essential steps in ensuring the well-being of our patients.
A cross-sectional study to determine the prevalence of insulin resistance and its relationship with patient and illness factors in schizophrenia patients in Hospital UKM was carried out using the HOMA model.

MATERIALS AND METHODS

The sample population was the patients with schizophrenia who attended the HUKM psychiatric department for inpatient and outpatient treatment. Patients were recruited by convenient sampling between March and September 2004. The sample comprised of patients aged 18-65 with a primary diagnosis of schizophrenia and confirmed using Structured Clinical Interview for DSM-IV (SCID)[9]. They had to be either drug-naïve or compliant on antipsychotic therapy (conventional or atypical) for at least three months. This research project was approved by the UKM Faculty of Medicine's Research and Ethics Committee and written informed consent was obtained. Patients with factors which could affect insulin resistance were excluded, such as current substance use, having any endocrine disorder other than diabetes mellitus or insulin/steroidal pharmacotherapy. Information on patient's baseline characteristics, illness(es), medication(s) and lifestyle was sought from the patient, caregiver (where available) and patient's notes. Severity of psychosis was measured using Brief Psychiatric Rating Scale (BPRS)[10]. Patient's weight, height and waist circumference were measured. Blood samples were taken after at least eight hours of fasting. Two mls of blood was collected in fluoride oxalate bottle to be processed via chemistry method using Cobas Integra 700 (Roche Diagnostics) to yield fasting plasma glucose (mmol/L). Patient's diabetic status was based on fasting plasma glucose [11] or if they had been diagnosed to have diabetes previously and were currently on oral hypoglycaemic agents. For fasting serum insulin (μIU/ml), 3 mls of blood was collected in a plain tube, centrifuged at 3000 rpm for 10 minutes and frozen at –20 degrees Celsius. The samples were processed via chemiluminescent method using Immulite from DPC. The intra-assay coefficient of variation was 5.2-6.4% while the interassay coefficient of variation was 5.9-8%.

Insulin Resistance (IR) was calculated using HOMA given by:

HOMA-IR = [fasting insulin (μIU/ml) x fasting glucose (mmol/L)]/22.5

Values above 1.21 (median insulin resistance in normal subjects from the original study[7]) were considered to be insulin resistant. Data analysis was done using the Statistical Package for Social Studies (SPSS) Version 12.0. Continuous data such as age, body mass index (BMI), waist circumference and BPRS score was tested for association with HOMA-IR

This article was accepted: 5 July 2007
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index values using linear regression. Categorical data such as sex, family history of diabetes, treatment with antipsychotic and type of antipsychotic was tested for association with status of insulin resistance (above or below 1.21) using non-parametric tests such as chi-square test and Fisher's exact test. Multivariate analysis was done using multiple linear regression.

RESULTS

Six hundred and thirty-eight patients were screened and 312 patients fitted inclusion criteria, but 227 (73%) patients could not be included mainly because of refusal to participate (199/227, 88%), language barrier (15/227, 7%) and severe cognitive impairment (2/227, 1%). Eleven patients had incomplete results. Therefore, complete results for only 85 patients were available, of which 74 were outpatients and 11 were inpatients. There was no significant difference between respondents and non-respondents in terms of age, sex, ethnicity, antipsychotic treatment and prevalence of known diabetes (9%). Table I shows the baseline characteristics of the sample.

The mean age of the patients was 37 years (SD 11). There were 45 male and 40 female patients. Although more than half of the patients were single (n = 61, 72%), most of the patients were living with their families (n = 80, 94%). The mean duration of illness in these patients was 12 years (SD 8). Mean BPRS score was 13 (SD 7) and 88% (n = 75) of the patients had minor syndrome or less. Table II shows the breakdown of patients' antipsychotic medication.

There were about equal numbers of patients on atypical (n= 40) and conventional antipsychotics (n = 41) but very few drug-naïve patients (n = 4) could be recruited. For the 81 patients who were on antipsychotics, mean duration on the current antipsychotic was 33 months (SD 31). The mean total duration of antipsychotics the patients had been on since they became ill was 10 years (SD 9). Thirteen patients were on combination conventional antipsychotics, mostly on one oral and one depot antipsychotic. For the atypical antipsychotics, most of the patients were on clozapine (n = 17) and olanzapine (n = 15). The doses of the antipsychotics were converted to chlorpromazine equivalent doses [12,13]. Mean dose of conventional antipsychotics in chlorpromazine equivalents was 300mg (SD 240) while for atypical antipsychotics it was 500mg (SD 330). The overall mean chlorpromazine equivalent dose was 400mg (SD 300).

Thirty percent (n = 26) of the patients were known to have at least one chronic metabolic illness while 66% (n = 56) of the patients were on other medications besides antipsychotics. Confounding factors, such as other illnesses (e.g. polycystic ovarian syndrome) and other medications (e.g. sodium valproate, traditional medication) which might have a direct or indirect effect on insulin resistance could not be completely excluded.

Comparable to other studies [1,2,3], 15% of the patients (n = 13) were diabetic while another 15% (n = 13) had impaired fasting glycaemia. Twenty-nine percent (n = 25) of the patients had family history of diabetes in a first degree relative. The mean HOMA-IR value was 2.37 (SD 1.79). Using the HOMA model, 68% (n = 58) of the patients had HOMA-IR values more than 1.21, and therefore, considered insulin resistant and at risk of developing diabetes.

Univariate analyses found BMI and waist circumference, but not the rest of the factors, to be associated with insulin resistance (see Table III). The statistical significance disappeared after multivariate analyses. However, p value for waist circumference approached significance (p = 0.09).

DISCUSSION

Sixty-nine percent of suitable patients could not be included in the study with refusal to participate cited as the main reason. Refusal to participate was due to several reasons, including difficulty coming for the tests, fear of blood tests, inability to fast, blood having been checked recently, lack of interest to participate and refusal on the part of the family. This was despite giving them ample time to come (6-month collection period), providing a token payment for transport and informing them of their results. Patients with schizophrenia are often reluctant to give consent to participate in studies especially those requiring blood samples[14]. Those who do consent may come from a self-selecting population and therefore do not necessarily represent an accurate picture. Therefore, selection bias cannot be excluded. Even when they do consent, researchers struggle to successfully complete the tests or to obtain true fasting values [14].

In the sample, even though more than half of the patients were single, more than ninety percent lived with their families. This means that theoretically, their families would be able to help monitor and support during any lifestyle intervention. BPRS scores revealed most of the patients (88%) had minor syndrome or less. Therefore, this may be a confounding factor when analysing for severity of psychosis. There were about equal numbers of patients on atypical and conventional antipsychotics respectively, sufficient for analysis. We are unable to conclude much from the drug-naïve group. Only a small number of patients could be recruited for that group mainly because of instability of diagnosis in the early stages of the psychotic illness and the practice of starting antipsychotics early in psychosis, regardless of exact diagnosis. It is crucial to study drug-naïve patients to exclude the influence of medication on weight and insulin resistance. Other researchers have been more successful at recruiting drug-naïve patients, although sample sizes were still small. Ryan *et al* [15] managed to recruit 26 drug-naïve patients and found 15% had impaired fasting glucose. They were also found to be more insulin resistant compared to healthy subjects.

Allowing for an increase since then, the prevalence of diabetes mellitus in Malaysia was 8.3% in 1996 [16]. We found the rate to be almost double in this group of patients. At a mean age of 37 years, this is a relatively young group of patients, certainly younger than the age recommended for type 2 diabetes screening by the American Diabetes Association (2004)[11], which is at age 45 years.

This study found 68% (n = 58) of the patients were insulin resistant and at risk of developing diabetes. Other studies

Table I: Baseline characteristics of the sample.

Variables	Number (n=85)	Percentage (%)
Ethnic group		
Malay	33	39
Chinese	35	41
Indian	17	20
Sex		
Male	45	53
Female	40	47
Marital status		
Single	61	72
Married	24	28
Employment		
Employed	53	62
Unemployed	32	38
Living circumstances		
With family	80	94
With non-relative	3	4
Alone	2	2

Table II: Patients' antipsychotic medication

Antipsychotic	Number (n=85)	Percentage (%)
Atypical	**40**	**47**
Clozapine	17	
Olanzapine	15	
Risperidone	7	
Combination (Risperidone & Quetiapine)	1	
Conventional	**41**	**48**
Trifluoperazine	1	
Flupenthixol	1	
Zuclopenthixol	1	
Flupenthixol depot	2	
Fluphenazine depot	3	
Haloperidol	3	
Chlorpromazine	3	
Thioridazine	4	
Sulpiride	10	
Combination	13	
Drug-naïve	**4**	**5**

Table III: Univariate analysis of patient and illness factors

Factors	p-value	(95% CI for B)
BMI	<0.001*	(0.132 to 0.265)
Waist circumference	<0.001*	(0.057 to 0.115)
Age	0.373	(-0.019 to 0.50)
Sex	0.207	
Family history of diabetes	0.630	
Severity of psychosis	0.065	(-0.105 to 0.003)
Antipsychotic treatment	0.589	
Type of antipsychotic	0.868	

have also shown increased insulin resistance but it is difficult to make comparisons with them because of differences in methodology used in the studies[17]. This study was not able to elicit significant differences between conventional and atypical antipsychotic therapy, possibly due to the small numbers. However, experts on the subject have particular concern for those on olanzapine and clozapine, while the risk in patients taking risperidone and quetiapine is less clear[18].

In this study, BMI and waist circumference were the factors which came closest to significance in terms of risk factors. This means psychiatrists need to manage these patients as a group at high risk for development of diabetes and include body weight management in their patient care. Baseline random/fasting glucose, fasting serum lipids and HbA1c are recommended, to be repeated after regular intervals, perhaps quarterly or after four months of treatment[18].

In this study, confounding factors such as co-morbid physical illness and concomitant medications could not be completely excluded. However, the main criticism of this study is that the cut-off point for insulin resistance used in this study may be over-inclusive. Despite this, it may still be justifiable, considering the high rate of type 2 diabetes found and the many possible risk factors in this group.

CONCLUSION

All patients with schizophrenia should be screened and managed as a group at high risk for development of diabetes with emphasis on body weight management. Better-designed, prospective studies are required in this area.

ACKNOWLEDGEMENTS

This study was funded by UKM faculty grant; project code: FF-017-2004.

REFERENCES

1. Subramaniam M, Chong SA, Pek E. Diabetes mellitus and impaired glucose tolerance in patients with schizophrenia. Can J Psychiatry 2003; 48: 345-47.
2. Sernyak MJ, Leslie DL, Alarcon R *et al*. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 2002; 159: 561-66.
3. Mukherjee S, Decina P, Bocola V, Saracini F, Scapicchio PL. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996; 37: 68-73.
4. Haddad PM. Antipsychotics and diabetes: review of non-prospective data. Br J Psychiatry 2004; 184: suppl. 47: 80-86.
5. Marques-Vidal P, Mazoyer E, Bongard V *et al*. Prevalence of insulin resistance syndrome in Southwestern France and its relationship with inflammatory and hemostatic markers. Diabetes Care 2002; 25: 1371-377.
6. Reaven GM. Banting Lecture 1988: Role of Insulin Resistance in Human Disease. Diabetes 1988; 37: 1595-607.
7. Matthews DR, Hosker JP, Rudenski AS *et al*. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-19.
8. Wallace TM, Jonathan, CL, Matthews DR. Use and Abuse of HOMA modelling. Diabetes Care 2004; 27: 1487-95.
9. Spitzer RL, Williams JBW, Gibbon M, First MB. Structured Clinical Interview for DSM III-R. Washington, D.C.: American Psychiatric Press, 1990.
10. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10: 799-812.
11. American Diabetes Association. Clinical Practice recommendations. Position Statements: Screening for Diabetes. Diabetes Care 2004; 27: s11-s14.
12. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Schizophrenia. Am J Psychiatry 1997; 154:(April suppl).
13. The South London and Maudsley NHS Trust. 2003 Prescribing Guidelines. 7th ed. London: Martin Dunitz.
14. Bushe C, Holt R. Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia. Br J Psychiatry 2004; 184: suppl. 47: 67-71.
15. Ryan M, Collins P, Thakore J. Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. Am J Psychiatry 2003; 160: 284-89.
16. Khalid BAK, Wan Nazaimoon WM, Ismail IS. The spread of diabetes mellitus in South-east Asia. Journal of the Asean Federation of Endocrine Societies 2001; 19: 14-19.
17. Newcomer, JW, Haupt DW, Fucetola R *et al*. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Arch Gen Psychiatry 2002; 59: 337-45.
18. Consensus Development Conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004; 27: 596-601.