Metabolic syndrome in type 1 diabetes

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Abstract

Objectives: The aim of this study was to assess the prevalence and effects of the presence of metabolic syndrome in patients with type 1 diabetes.

Research design and methods: Retrospective analysis of data from a one year period of patients attending annual review clinic was undertaken. Body weight, height and blood pressure were measured along with assessment of micro-/macro-vascular complications. HbA1c, urea, cholesterol, triglyceride, urinary albumin: creatinine ratios were also measured. Patients were divided into those with and those without metabolic syndrome.

Results: Data from 365 type 1 diabetic patients was analysed. Hundred and twelve had metabolic syndrome. There was no difference according to gender or smoking. Type 1 diabetic patients with metabolic syndrome had longer duration of diabetes, were significantly older, heavier, had higher blood pressure, higher triglyceride and lower HDL cholesterol levels. There were significant increases in mean BMI, urea, serum creatinine, urinary albumin: creatinine ratio, cholesterol and triglyceride in the group with metabolic syndrome even after controlling for both age and duration of diabetes. Neuropathy and macro-vascular complications were commoner in patients with metabolic syndrome. Patients with metabolic syndrome were more likely to be on statins, ACE inhibitors and angiotensin receptor blockers and had a significantly higher mean insulin dosage requirement per kg.

Conclusions: This study highlights the importance of the presence of metabolic syndrome in patients with type 1 diabetes. It shows that metabolic syndrome is associated with a higher incidence of diabetes-related complications, a need for higher insulin doses and a more aggressive multifactorial intervention.

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1. Background

Metabolic syndrome, for which there are multiple definitions, consists of a clustering of cardiovascular risk factors. The most recent definition is the consensus document from the International Diabetes Federation (IDF) [1]. The World Health Organisation (WHO), National Cholesterol Education Program (NCEP) and the Adult Treatment Panel (ATP) III have each proposed different criteria for the diagnosis of the metabolic syndrome [2–5].

The presence of metabolic syndrome is considered to be an important risk factor for cardiovascular disease and mortality in patients with type 2 diabetes and non-diabetic subjects [6–9]. The phrase “double diabetes” has recently been coined for those patients who have type 1 diabetes and insulin resistance [10,11]. Recent studies suggest that these patients appear to be at increased risk of developing macro- and micro-vascular complications [12–15].

The aim of this study was to assess the prevalence and effects of metabolic syndrome in type 1 diabetic patients in a Scottish population. The study also reviewed the prevalence of macro- and micro-vascular complications, differences in metabolic parameters and the types of medications that these patients received. Statistical analysis was carried out to determine whether the prevalence of complications and the differences in the clinical and biochemical parameters were significantly different between those with and without metabolic syndrome.

2. Research design and methods

The study was undertaken at the Diabetes Day Centre, The Ayr Hospital, which is a District General Hospital in Scotland, UK. A comprehensive annual review is undertaken on all diabetic patients attending the clinic. Body weights of patients are recorded (in kg) using electronic scales (SECA, Birmingham, UK). Height was measured in meters using a (? ) Harpenden Stadiometer. Blood pressure was recorded using a standard sphygmomanometer. Fundal photography was undertaken with pupils dilated (TopconTRC-NW6 Digital Retinal Camera (www.topcon.co.uk) fitted with a Nikon D70 (www.nikon.co.uk)) and formally assessed by trained graders.

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Assessment for peripheral neuropathy was performed by testing using a 10 g nylon monofilament, and ankle reflexes were checked. Peripheral vascular disease was considered to be present if pedal pulses were non-palpable or undetectable by a hand held Doppler or if there was history of claudication and/or rest pain. Ischaemic heart disease was documented as the presence of a history of angina, myocardial infarction or coronary revascularisation procedures. This was confirmed from history, clinical notes or investigations (such as ECG/ETT/Angiography). Similarly, history of stroke or Transient Ischaemic Attack was confirmed from history, clinical notes or investigations (such as neuroimaging).

Venous blood was taken for the measurement of HbA1c using HPLC (Menarini–Arkray HA 8140 haemoglobin A1c analyzer, Menarini diagnostics, Wokingham, UK; intra-assay CV 1.9%). Blood urea, serum creatinine, urinary albumin and creatinine, cholesterol and triglyceride were measured using Roche Modular Analyzer (Basel, Switzerland). Urine albumin concentration was measured by radioimmunoassay, CV < 9%. Urinary creatinine concentration was measured by an end point Jaffe reaction, CV < 6%.

Data was entered into the hospital-based SCI-DC database (Scottish Care Information – Diabetes Collaboration, www.DiabetesinScotland.org). We performed a retrospective analysis of our Diabetes Centre Database. For the purposes of this study, the computerised database was used to retrieve the data obtained for all patients attending the diabetes clinic for the year 2007. The database contains information on patient demographic, diabetic complications, metabolic parameters and medications. Patients in whom the diagnosis of type 1 diabetes was uncertain and in whom data collection was incomplete were excluded from the study.

We used the WHO Criteria for the definition of the metabolic syndrome. The WHO criterion uses either Body Mass index (BMI) ≥ 30 kg/m² to define obesity, or waist circumference for the diagnosis of metabolic syndrome [16]. We used BMI data for the diagnosis of obesity as this was the recording available from the database.

As all our patients were diabetic, patients were classified as having metabolic syndrome if two or more of the following criteria were present:

- Obesity as defined by BMI ≥ 30 kg/m².
- Dyslipidaemia: triglyceride ≥ 1.7 mmol/l or HDL cholesterol <0.9 in males or <1.0 in females (mmol/l).
- Hypertension: BP ≥140/90 mm Hg or on treatment.
- Microalbuminuria: (albumin:creatinine ratio) male ≥2.5; female ≥ 3.5 (mg/mmol).

Using the above criterion the patients, were divided into those with and those without metabolic syndrome.

3. Statistical analysis

SPSS (Social Package for Statistical Sciences) version 15 was used to analyse the data obtained.

As both age and duration of diabetes are important extraneous variables, the analysis of the effect of metabolic syndrome on interval level variables was carried out using analysis of covariance (ANCOVA) with group membership as the fixed factor with age and duration as covariates.

For categorical variables, hierarchical logistic regression was carried out to assess the effect of metabolic syndrome. In the regression models, age and duration are added as independent variables in the first block and metabolic syndrome is added in the second block in order to determine the incremental improvement in fit when adding group membership after the effects of age and duration are taken into account.

4. Results

4.1. Comparison of baseline data (Table 1)

Data from 365 type 1 diabetic patients was analysed. 9.3% patients were obese, 34.0% had dyslipidaemia, 27.4% had hypertension and 21.4% had microalbuminuria. Hundred and twelve patients fulfilled the criteria for metabolic syndrome. There was no difference according to gender or smoking status. Type 1 diabetic patients with metabolic syndrome were significantly older and had a significantly longer duration of diabetes. They were also heavier, had higher blood pressure, higher triglyceride and lower HDL cholesterol levels than their non-metabolic syndrome counterparts.

Analysis of covariance showed that there were significant increases in mean BMI and triglyceride in the group with metabolic syndrome after controlling for both age and duration.

### Table 1

Baseline and demographic data of the two groups of patients in terms of gender, age, duration of diagnosis, plus Body Mass index (BMI), triglycerides, High Density Lipoprotein (HDL) and hypertension.

<table>
<thead>
<tr>
<th></th>
<th>With metabolic syndrome</th>
<th>Without metabolic syndrome</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>112</td>
<td>253</td>
<td></td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>55.43 (20.35)</td>
<td>38.62 (15.82)</td>
<td>t(362) = 8.54, p &lt; 0.01</td>
</tr>
<tr>
<td>Mean duration of diabetes in years (SD)</td>
<td>21.58 (13.38)</td>
<td>17.92 (12.58)</td>
<td>t(356) = 2.48, p &lt; 0.05</td>
</tr>
<tr>
<td>Males (%)</td>
<td>56.3</td>
<td>56.1</td>
<td></td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>42 (37.8%)</td>
<td>92 (36.7%)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI (kg/m²) (SD)a</td>
<td>26.74 (3.96)</td>
<td>24.74 (3.23)</td>
<td>F(1, 345) = 21.22, p &lt; 0.01</td>
</tr>
<tr>
<td>Mean triglyceride (mmol/l) (SD)a</td>
<td>2.36 (1.29)</td>
<td>1.24 (0.67)</td>
<td>F(1, 347) = 99.91, p &lt; 0.01</td>
</tr>
<tr>
<td>Mean HDL (mmol/l) (SD)a</td>
<td>1.45 (0.43)</td>
<td>1.73 (0.46)</td>
<td>F(1, 340) = 23.87, p &lt; 0.01</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>72.3%</td>
<td>75.5%</td>
<td></td>
</tr>
</tbody>
</table>

* Estimated marginal means are evaluated at the mean values for covariates of length of diagnosis and age.

### Table 2

The biochemical parameters measured in the two groups.

<table>
<thead>
<tr>
<th></th>
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<th>Without metabolic syndrome</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>112</td>
<td>253</td>
<td></td>
</tr>
<tr>
<td>Mean urea (mmol/l) (SD)a</td>
<td>7.54 (4.19)</td>
<td>5.77 (2.01)</td>
<td>F(1, 347) = 27.06, p &lt; 0.01</td>
</tr>
<tr>
<td>Mean creatinine (μmol/l) (SD)a</td>
<td>122.39 (61.69)</td>
<td>96.55 (15.95)</td>
<td>F(1, 345) = 31.19, p &lt; 0.01</td>
</tr>
<tr>
<td>Mean cholesterol (mmol/l) (SD)a</td>
<td>5.21 (1.03)</td>
<td>4.71 (0.95)</td>
<td>F(1, 347) = 15.65, p &lt; 0.01</td>
</tr>
<tr>
<td>Mean LDL (mmol/l) (SD)a</td>
<td>2.64 (0.92)</td>
<td>2.43 (0.83)</td>
<td>F(1, 327) = 3.49, p = 0.06</td>
</tr>
<tr>
<td>Mean albumin:creatinine (mg/mmol) (SD)a</td>
<td>8.99 (9.46)</td>
<td>2.01 (3.86)</td>
<td>F(1, 305) = 72.94, p &lt; 0.01</td>
</tr>
</tbody>
</table>

* Estimated marginal means are evaluated at the mean values for covariates of length of diagnosis and age.
Table 3
Prevalence of complications in the two groups.

<table>
<thead>
<tr>
<th></th>
<th>With metabolic syndrome</th>
<th>Without metabolic syndrome</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>112</td>
<td>253</td>
<td></td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>25 (22.3%)</td>
<td>10 (4.0%)</td>
<td>$\chi^2(1) = 15.26, p &lt; 0.01$</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>12 (10.7%)</td>
<td>25 (9.9%)</td>
<td>$\chi^2(1) = 0.15, p &gt; 0.70$</td>
</tr>
<tr>
<td>IHD/MI (%)</td>
<td>27 (24.1%)</td>
<td>10 (4.0%)</td>
<td>$\chi^2(1) = 4.24, p &lt; 0.05$</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>6 (5.4%)</td>
<td>5 (2.0%)</td>
<td>$\chi^2(1) = 0.06, p &gt; 0.81$</td>
</tr>
</tbody>
</table>

4.2. Comparison of the biochemical parameters (Table 2)

Those with metabolic syndrome had significantly higher mean levels of urea, serum creatinine, urinary albumin: creatinine ratio and total cholesterol levels after controlling for both age and duration of diabetes. Patients with metabolic syndrome had a higher mean LDL-cholesterol, but the difference was not significant.

4.3. Comparison of prevalence of complications (Table 3)

Macro-vascular complications such as ischaemic heart disease/myocardial infarction (IHD) was more common in patients with metabolic syndrome as was neuropathy.

Difference in the prevalence of retinopathy or stroke in patients with metabolic syndrome failed to reach levels of statistical significance.

4.4. Comparison of the use of medication in the two groups (Table 4)

Patients with metabolic syndrome were more likely to be on statins, ACE inhibitors and angiotensin receptor blockers. Only two patients were on fibrates, and while both were in the metabolic syndrome group the numbers were too small.

Finally, an analysis of covariance showed that patients with metabolic syndrome had a significantly higher mean insulin dose requirement per kg after controlling for age and duration.

5. Conclusions

In our cross-sectional study, metabolic syndrome was evident in ~30% of type 1 diabetic patients, which is similar to that of the FinnDiabe study. The FinnDiabe study, which used NCEP criteria, demonstrated that 38% of men and 40% of women with type 1 diabetes had metabolic syndrome [17,18]. The DCCT Follow-up group and the Pittsburgh Epidemiology of Diabetes Complications study groups had a lower prevalence (between 8% and 22%). In the Pittsburgh Epidemiology of Diabetes Complications study groups, metabolic syndrome was most commonly found with the IDF criteria, and less so with AHA/NCEP criteria [19]. The different definitions used understandably give differing prevalence of metabolic syndrome in type 1 diabetes [20].

The metabolic syndrome generally predicts an adverse outcome and the risk of developing major micro- and macro-vascular complications, but the prevalence obviously varies according to the definition used. Microalbuminuria, which is a criterion in some definitions of the metabolic syndrome, seems to be the best marker of prediction for the development of micro- and macro-vascular complications [21]. Microalbuminuria appears to reflect both insulin resistance, which is central to both the concept of the metabolic syndrome, and vascular damage, as originally postulated by the Steno Group [22].

Cardiovascular disease is one of the leading causes of morbidity and mortality in Scotland, in part due to the increasing prevalence of obesity [23]. Obesity is a major public health concern, with more than 40% of the adult population in the industrialised world being overweight or clinically obese [24]. The reasons for the dramatic increase in obesity are complex, and include lifestyle changes plus demographic and political factors [25]. It seems likely that the prevalence of obesity in type 1 diabetes parallels the prevalence of obesity in the general population. With this increase, there is also an increased chance of clustering of cardiovascular risk factors including hypertension, dyslipidaemia, central obesity and low physical activity, all of which are associated with insulin resistance and contribute to the metabolic syndrome. Hence, it comes as no surprise that a significant proportion of our patients with type 1 diabetes fulfilled the criteria for the metabolic syndrome.

In our study, patients with metabolic syndrome were older, and had a longer duration of diabetes. As these type 1 patients would obviously have been younger and probably also leaner at diagnosis, our study probably under-estimates the effect of the risk factors that make up metabolic syndrome. Despite this under-estimation, our study clearly demonstrates a much higher prevalence of complications in this group of patients. Even after adjustment for age and duration of diabetes, these patients were more likely to have hypertension, dyslipidaemia and worse glycaemic control. In addition, the risk of developing macro-vascular complications such as ischaemic heart disease, myocardial infarction and peripheral vascular disease, along with micro-vascular complications such as nephropathy and neuropathy, were higher in the group with metabolic syndrome, despite receiving much greater therapeutic interventions.

Longitudinal studies, such as the Pittsburgh study and the DCCT Follow-up, clearly showed that patients with type 1 diabetes gain weight with time. It would seem likely that this weight gain would be associated with an increase in the prevalence of the metabolic syndrome [26-29]. However, the DCCT Follow-up study showed that the intensively treated group fared better with diabetes-related outcomes despite the weight gain. It would appear from this study that the long-term benefits of good glycaemic control outweigh the deleterious effects of weight gain associated with the treatment of diabetes [30].

Even with relatively small numbers, our study demonstrates an increase in the prevalence of neuropathy and nephropathy in patients with metabolic syndrome confirming the findings of previous studies, including the Metascreen study [31]. Previous studies have demonstrated that the risk of stroke is higher in patients with type 1 diabetes with metabolic syndrome.[32] Our study demonstrated that in patients with the metabolic syndrome patients there was a threefold increase in the prevalence of stroke; however this did not reach levels of statistical significance.

The prevalence of retinopathy in our study was not increased in those with metabolic syndrome. Our results are similar to the
findings of previous studies [33]. The reasons for this are not clearly understood.

Our patients with metabolic syndrome were on higher doses of insulin per kg of body weight, and yet achieved poorer glycaemic control, implying that even higher doses of insulin would have been required to achieve comparable glycaemic control. This is clearly in keeping with the concept that insulin resistance being a key feature of metabolic syndrome [34]. Other studies have also demonstrated that patients who are overweight/obese with metabolic syndrome have higher insulin requirements [35].

In type 2 diabetic patients, metformin provides cardiovascular protection reducing all-cause mortality by 36% and myocardial infarction by 39% [36]. The mechanism of action is not clearly understood, but it is suggested that metformin has significant effects on several markers of endothelial and thrombolytic function with reductions in vascular cell adhesion molecule, plasminogen activator inhibitor-1 and tissue plasminogen activator [37,38]. In addition, other studies have demonstrated that the use of metformin can improve glycaemic control, and reduce total daily insulin dosage in overweight and adolescent type 1 diabetic patients [39]. Similarly there are small studies with the use of rosiglitazone in overweight subjects with type 1 diabetes which have demonstrated improved glycaemic control with lower insulin requirements [40].

Our study highlights the importance of the presence of the metabolic syndrome in patients with type 1 diabetes and clearly demonstrated that the metabolic syndrome is associated with a higher incidence of diabetes-related complications, a greater need for higher insulin doses and more aggressive treatment (multifactorial intervention). We would suggest that the presence of the metabolic syndrome should be used as a clinical marker of insulin resistance and that these patients should be encouraged to intensify lifestyle changes and should be considered for insulin sensitizers such as metformin. We would hope that this would lead to a reduction in total daily insulin requirements, better glycaemic control, better clinical outcomes and fewer diabetes-related complications.

References