The metabolic syndrome, incidence of diabetes and mortality among the elderly: The Italian Longitudinal Study of Ageing


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Abstract

Aim. – To investigate whether or not the metabolic syndrome (MetS) can predict the incidence of diabetes and all-cause mortality among elderly subjects.

Methods. – Analyses were based on data collected by the Italian Longitudinal Study on Aging (ILSA) that, between 1992 and 1996, enrolled 5632 participants aged 65 to 84 years. The analyses included 3081 participants for whom complete data were available. Logistic-regression models were designed to study the influence of the MetS on the incidence of diabetes, adjusting for individual MetS components and possible confounders. Data on mortality collected between baseline and the 1996 follow-up were also considered, and Cox’s proportional hazards models were used to determine the death risk attributable to the synergistic relationship between the MetS and diabetes.

Results. – The MetS was strongly associated with an increased risk of diabetes (OR: 5.53, 95% CI: 2.89–10.60). After adjusting for its individual components and possible confounders, the MetS maintained an important role in predicting the incidence of diabetes (OR: 2.65, 95% CI: 0.97–7.24) together with the fasting glucose component (OR: 5.89, 95% CI: 2.89–11.98). Over the 4-year follow-up, participants with diabetes, but without the MetS, and subjects with the MetS, but without diabetes, had no significant risk of death compared with the reference group. Elderly subjects who had both the MetS and diabetes had almost double the risk of death vs the reference group (HR: 1.80, 95% CI: 1.04–3.12).

Conclusion. – The MetS is associated with the incidence of diabetes, and the synergy between the MetS and diabetes is an important risk factor for all-cause mortality in elderly subjects.

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Keywords: The metabolic syndrome; Diabetes; Mortality; Elderly

Résumé

Syndrome métabolique, incidence du diabète et mortalité chez les sujets âgés. Étude ILSA (The Italian Longitudinal Study of Ageing).

Objectifs. – Déterminer si l’existence d’un syndrome métabolique (SM) permettait de prévoir l’incidence du diabète et la mortalité totale chez des sujets âgés.


Résultats. – Le SM était étroitement associé au développement du diabète (OR = 5,53, IC à 95 %: 2,89–10,60). Même après ajustement sur les facteurs confondants potentiels, la valeur prédictive du SM persistait pour l’incidence du diabète (OR = 2,65, IC à 95 %: 0,97–7,24) et pour la glycémie à jeun (OR = 5,89, IC à 95 %: 2,89–11,9). Au cours des quatre ans de suivi, les participants atteints de diabète mais sans SM et les patients avec SM indemnes de diabète n’ont pas présenté d’augmentation de mortalité par rapport au groupe de référence. Les sujets âgés qui présentaient l’association SM–diabète ont vu doubler leur risque de décès par rapport au groupe de référence (HR = 1,80; IC 0 95 %: 1,04–3,12).

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1. Introduction

The metabolic syndrome (MetS), a cluster of metabolic and physiological disorders that increases the risk of developing cardiovascular disease and diabetes, was first described more than 40 years ago [1]. Since then, various definitions of the syndrome have been proposed, with those of the World Health Organization (WHO), International Diabetes Federation (IDF) and National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) being among the most common [2–4].

The MetS affects an important percentage of Italian adults, ranging from 15–29% among men and 18–27.2% among women [5–7]. The prevalence of the MetS increases with age, and the results of the Italian Longitudinal Study on Aging (ILSA) show that it is present in 31.5% of older men and 59.8% of older women [8]. Further analyses using data from the ILSA study have confirmed that the diagnostic criteria proposed by the ATP-III panel were appropriate for older individuals [9], and that the MetS is associated with chronic heart disease and cardiovascular mortality in men [8]. Also, other studies conducted in Italy involving a sample of elderly subjects have confirmed the association of the MetS with all-cause and cardiovascular mortality [10].

Prevalence and incidence rates of type 2 diabetes (T2D) are growing throughout most regions of the world [11], and the emergence of such a “diabetes pandemic” is attributable to established causes such as ageing of the population, and growing levels of obesity and physical inactivity [12]. T2D increases the risks of eyesight problems, kidney dysfunction, neurological impairment, coronary heart disease, vascular disease, and physical and cognitive disabilities, and is a major global cause of premature mortality. Because of its association with insulin resistance, subjects with the MetS are more likely to have both prevalent and incident T2D, and data are available mostly for adult populations [13].

The aim of the present work was to investigate whether or not the MetS can predict the incidence of T2D and whether or not there is a synergistic relationship between MetS–T2D and all-cause mortality in elderly subjects.

2. Patients and methods

2.1. Study population

All analyses were performed with data from ILSA, an epidemiological study conducted in Italy and described in detail elsewhere [14]. A random sample of 5632 individuals aged 65 to 84 years, stratified by age and gender using an equal-allocation strategy, was selected from the population registries of eight Italian municipalities. The study protocol, approved by the ethics committees of the participating centres, and the aims of the study were explained to each subject before they gave their written informed consent.

The baseline survey (1992) was organized into two phases: phase 1 involved all participants, and included a standardized interview for health-related behaviours and medical history, laboratory tests using a blood sample taken after an overnight fast and selected diagnostic tests; and phase 2, involving only those subjects who screened positive in phase 1, consisted of clinical confirmation of suspected cases of cardiovascular disease, diabetes, parkinsonism, stroke, dementia and peripheral neuropathy as a result of examination by a specialist and review of the patients’ clinical records [15]. In particular, participants with a self-reported diagnosis of diabetes, or receiving treatment for diabetes or with a fasting glycaemia ≥ 140 mg/dL in phase 1 were evaluated by an internist who reviewed all available medical records. Those with a fasting glycaemia ≥ 140 mg/dL, but without a positive history, were considered positive only if their levels were confirmed on a second blood determination. Physical functioning was assessed by the self-reported degree of difficulties scores in the Activities of Daily Living Scale (ADL) [16] and Instrumental Activities of Daily Living Scale (IADL) [17].

The ILSA study had two follow-up periods: 1995–1996 and 2000. A copy of the official death certificate was obtained for each participant who died between baseline and the follow-ups.

2.2. Assays of blood samples

Plasma lipids and glucose were measured using the standard enzymatic methods. Low-density lipoprotein (LDL) cholesterol was calculated by Friedewald’s equation, whereas insulin was measured by radio-immunoassay, and fibrinogen and haemoglobin by electrophoresis; cell blood counts were performed using an automated counter.

2.3. Anthropometric measures

Anthropometric measurements were taken by trained personnel during the clinical evaluation. Height and weight were measured with the subjects barefoot and lightly dressed. Body weight was measured on a balance beam platform scale (Salus, Milan, Italy) to the nearest 0.1 kg. Height was measured by a stadiometer (Salus) at head level to the nearest cm with the subject standing barefoot with feet together. Circumferences were measured to the nearest cm, using a flexible steel tape, with the subject standing. The abdominal circumference (waist) was measured at the end of expiration with the tape placed at the level of the umbilicus.
2.4. Definition of the metabolic syndrome

In accordance with ATP-III criteria, diagnosis of the MetS was established based on the presence of three or more of the following criteria: abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women); elevated plasma triglycerides (≥ 150 mg/dL); low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL in men and < 50 mg/dL in women); high blood pressure (≥ 130/≥ 85 mmHg); and high fasting plasma glucose (≥ 110 mg/dL). Criteria for the MetS also included taking lipid-lowering medications and/or antihypertensive treatment.

2.5. Statistical analysis

To generalize the ILSA sample to the Italian population, a set of weights was defined according to gender, age distribution of the reference population (1991 census) and sample fraction, and applied to the analyses. Incident cases of T2D at the 1996 follow-up were identified; the association of baseline characteristics and incidence of T2D was evaluated using the χ² or exact test for categorical variables. The difference between mean values for quantitative variables was evaluated through a generalized linear model. The MetS prevalence among elderly subjects without T2D at baseline and the prevalence of the individual MetS components were also calculated.

Logistic-regression models were designed to study the influence of the MetS on the incidence of T2D, adjusting for age, gender, individual MetS components and possible confounders, identified through a stepwise procedure based on education, smoking status, marital status, hypertension, myocardial infarction, heart failure, angina, stroke, distal symmetrical neuropathy, arrhythmia, claudication, and disability scores from the ADL and IADL.

Data on mortality collected between baseline and the 1996 follow-up were also included, while Cox’s proportional hazards models were used to determine the risk of death attributable to the synergy between the MetS and T2D, adjusting for possible confounders identified by a stepwise procedure. The assumption of proportionality was assessed through analysis of Schoenfeld residuals of covariates. For the analysis of mortality, subjects were classified into four groups:

- those without the MetS and T2D (reference group);
- those with T2D, but without the MetS;
- those with the MetS, but without T2D;
- those with both the MetS and T2D.

The analyses were carried out using SAS statistical software, version 9.2 (SAS, Cary, NC, USA).

3. Results

According to the availability of a T2D diagnosis (present vs not present), the baseline ILSA sample was divided into two groups: one with 1131 subjects (20.1%) who had not undergone a valid T2D diagnostic procedure at baseline; and the other with 4499 subjects (79.9%) who had. Of the subjects with valid T2D diagnoses, 3081 had complete information on the other covariates considered in the present analysis, and 421 presented with T2D at baseline (Fig. 1). Of the 2660 subjects without diabetes at baseline and with valid information on the other studied covariates, only 2221 subjects also had follow-up data for T2D (in other words, 439 subjects were lost to follow-up for the T2D incidence analysis).

Table 1 shows the baseline characteristics of the subjects (n = 68) who developed incident T2D over the follow-up period. Incident cases of T2D presented with significantly higher levels of mean fasting glucose (6.53 ± 1.17 mmol/L vs 5.33 ± 0.70 mmol/L for non-incident cases; P < 0.0001), a higher prevalence of hypertension (78.5% vs 63.8%; P = 0.0123), and higher mean values of systolic and diastolic blood pressure. Incident cases of T2D also presented with higher mean weight, body mass index (BMI) and waist circumference (P < 0.0001). In addition, prevalence rates of heart failure and stroke were higher for incident T2D cases than for non-incident cases (9.0% vs 5.0% and 11.2% vs 5.5%, respectively), and were of borderline significance (P ≤ 0.10).

Of those subjects without diabetes at baseline and who therefore were at risk of developing T2D at follow-up, the MetS was present in 49.3% of cases (Table 2). Single metabolic factors were present in different percentages of subjects: while the criteria for fasting glucose (≥ 5.6 mmol/L) were fulfilled in 34.8% of the elderly without diabetes at baseline, abdominal obesity was present in 53.1% and blood pressure criteria (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or the use of antihypertensive treatment) were present in 89%.

Table 3 presents the odds ratios (OR) and 95% confidence interval (CI) for incident cases of T2D associated with the MetS and its individual criteria. The syndrome was strongly associated with an increased risk of developing T2D after adjusting for gender and age only (Model 1: OR 5.53, 95% CI 2.89–10.60). Adjusting for MetS individual components and possible confounders maintained the strong association (Model 3: OR 2.65,
Non-diabetic subjects at baseline with the metabolic syndrome (MetS) and/or a fasting glucose (ATP-III: Third Report of the Adult Treatment Panel of the National Cholesterol Education Program; HDL: high-density lipoprotein.

Table 2
Baseline characteristics of the subjects with incident diabetes: the Italian Longitudinal Study on Aging (ILSA).

<table>
<thead>
<tr>
<th>Incident diabetes</th>
<th>Absent (n=2153)</th>
<th>Present (n=68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, men (%)</td>
<td>45.0</td>
<td>40.3</td>
<td>0.4478</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>72.3 ± 5.4</td>
<td>72.5 ± 5.6</td>
<td>0.7454</td>
</tr>
<tr>
<td>Education, elementary or less (%)</td>
<td>70.7</td>
<td>69.1</td>
<td>0.7631</td>
</tr>
<tr>
<td>Smoking status, current smoker (%)</td>
<td>14.5</td>
<td>15.7</td>
<td>0.7688</td>
</tr>
<tr>
<td>Systolic BP, mmHg (mean ± SD)</td>
<td>146.8 ± 20.3</td>
<td>154.6 ± 19.4</td>
<td>0.0019</td>
</tr>
<tr>
<td>Diastolic BP, mmHg (mean ± SD)</td>
<td>82.1 ± 10.1</td>
<td>86.2 ± 13.2</td>
<td>0.0177</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L (mean ± SD)</td>
<td>5.33 ± 0.70</td>
<td>6.53 ± 1.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L (mean ± SD)</td>
<td>5.70 ± 1.12</td>
<td>5.71 ± 1.24</td>
<td>0.9479</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L (mean ± SD)</td>
<td>1.28 ± 0.37</td>
<td>1.24 ± 0.31</td>
<td>0.4244</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L (mean ± SD)</td>
<td>3.69 ± 1.12</td>
<td>3.76 ± 1.20</td>
<td>0.6395</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (mean ± SD)</td>
<td>1.63 ± 0.85</td>
<td>1.56 ± 0.69</td>
<td>0.4689</td>
</tr>
<tr>
<td>Weight, kg (mean ± SD)</td>
<td>67.5 ± 12.7</td>
<td>74.0 ± 14.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m² (mean ± SD)</td>
<td>26.9 ± 4.5</td>
<td>29.1 ± 4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference, cm (mean ± SD)</td>
<td>96.5 ± 12.1</td>
<td>103.4 ± 11.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>63.8</td>
<td>78.5</td>
<td>0.0123</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>7.8</td>
<td>4.1</td>
<td>0.2588</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>5.0</td>
<td>9.0</td>
<td>0.0917</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>6.5</td>
<td>10.0</td>
<td>0.2017</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>5.5</td>
<td>11.2</td>
<td>0.1057</td>
</tr>
</tbody>
</table>

BP: blood pressure; HDL/LDL: high-/low-density lipoprotein; BMI: body mass index.

95% CI 0.97–7.24) together with the fasting glucose level (OR: 5.89, 95% CI: 2.89–11.98).

During the 4-year follow-up (1992–1996), 297 of the elderly subjects with or without T2D at baseline died (Table 4). According to the analysis classifications described above, four groups of elderly subjects were identified:

- 1529 without MetS–T2D (reference group);
- 92 with T2D, but without the MetS;
- 1132 with the MetS, but without T2D;
- 328 with MetS–T2D.

After adjusting for possible confounders, the elderly with T2D, but without the MetS, had no significant risk of all-cause mortality (HR: 0.81, 95% CI: 0.39–1.71), and those with the MetS, but without T2D, had no significantly higher risk of death compared with the reference group (HR: 1.13, 95% CI: 0.72–1.77). In contrast, elderly subjects with both the MetS and T2D had almost double the risk of death compared with the reference group (HR: 1.80; 95% CI: 1.04–3.12).

4. Discussion

The MetS has proved to be a good predictor of T2D in adult populations [13], but few studies have looked at its validity in the elderly [10]. Our present study reveals that some of the components of the MetS are commonly found in the aged population and, considered altogether, represent a major risk for developing T2D. In contrast, except for glycaemia, all the other components of the MetS do not increase the risk of T2D when considered individually. Our results show that impaired fasting glucose is a stronger predictor of T2D than the sum of the MetS traits; this is consistent with the results of a large number of studies [18–26]. However, the value added by the MetS is that it emphasizes the interaction between multiple risk factors, some of which are modifiable through changes in lifestyle [27]. Lorenzo et al. [28] showed that the MetS allowed further predictions beyond that provided by fasting hyperglycaemia in 2559 subjects aged 25 to 64 years. Our present study shows the same results in an older population.

Of particular interest are the findings related to triglycerides, a component of the MetS that, on its own, appears to have a protective effect against the development of T2D in older individuals. It is likely that the causes of raised triglyceride levels in the MetS in aged individuals are multifactorial [29]. A higher level of triglycerides could be associated with better nutritional status in aged individuals, considering that our study population, on average, had triglyceride levels below the cut-off value.
of 1.69 mmol/L in both those who developed T2D and those who did not. Moreover, in older patients, the combined presence of T2D and the MetS significantly increased the risk of death.

These results suggest that, when evaluating the mortality risks associated with T2D, those subgroups at high risk, such as MetS patients, should be identified. It was also found that neither the non-diabetic individuals with the MetS nor the diabetic patients without the MetS had an increased risk of death. However, elderly subjects with both T2D and the MetS had an almost threefold increased risk of mortality in our 4-year follow-up.

Nevertheless, our present study has some limitations. First, the latest criteria for the diagnosis of T2D were not used [30], as the prevalence rates of the disease were calculated in 1994 [14]. For this reason, individuals not previously diagnosed, and with fasting glycaemia between 126 and 139 mg/dL, were classified as non-diabetic. Given the potential for misclassification, we may have reported a stronger association between the MetS and mortality in non-diabetic individuals. However, even after excluding those individuals with glycaemia ≥ 126 mg/dL who did not undergo phase 2 for clinical confirmation of T2D, the results remained similar to those reported here.

Another limitation of our study is the number of subjects lost to follow-up for the incidence analysis compared with the number of incident cases: of the 2660 subjects without diabetes at baseline, data at follow-up for diabetes were available for only 2221 — in other words, 439 (16.5%) subjects were lost to follow-up for the T2D incidence analysis. Despite the large sample size at baseline and a mean follow-up duration of 3.2 years, the number of incident cases of diabetes and deaths in each group was small. Studies involving larger sample sizes with longer follow-up or a meta-analysis of data from the current literature are needed to confirm these results.

On the other hand, the strengths of our study include its population-based design with a sample that is representative of the older Italian population, the clinical diagnoses of diseases,
and the reliable assessment of metabolic and cardiovascular risk factors, and causes of death.

5. Conclusion

The MetS is frequently found in older Italians, in whom it increases the risk of diabetes and mortality. Therefore, its identification in older people, as demonstrated in younger adults, may represent a useful point for clinical interventions that can reduce the risks of morbidity and mortality.

It is our conviction that the MetS, which is present in epidemiologic differences among aged individuals, represents one of the major threats to longevity and healthy aging, and geriatricians need to be aware of the importance of preventing and, if already present, of managing this high-risk condition. Major challenges, however, remain in identifying those subgroups who are at greatest risk of developing T2D. From our present data, it may be concluded that the MetS is indeed “more than the sum of its parts, in predicting the development of T2D and in predicting mortality among older people with diabetes” [29].

The present work demonstrates that elderly patients with both T2D and the MetS have an almost threefold increased risk of mortality. For this reason, it is important to identify, among subjects with the MetS, those subgroups, such as T2D patients, at high risk of death.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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