# Metabolic Syndrome and Autoimmune Diabetes: Action LADA 3

Mohammed I. Hawa, bsc[1]
Charles Thivolet, md[2]
Didac Mauricio, md[3]
Irene Alemanno, md[1]
Elisa Cipponeri, md[1]
David Collier, md[1]

Steven Hunter, md[4]
Raffaella Buzzetti, md[5]
Alberto de Leiva, md[3]
Paolo Pozzilli, md[1,6]
Richard David G. Leslie, md[1]
on behalf of the Action LADA Group*

**OBJECTIVE** — The purpose of this study was to estimate whether prevalence of metabolic syndrome in adult European diabetic patients is associated with type of diabetes.

**RESEARCH DESIGN AND METHODS** — A consecutive series of patients attending hospital-based diabetes clinics were assessed for the frequency of metabolic syndrome and compared with population-based control subjects as part of the Action LADA study. In total, 2,011 subjects (aged 30–70 years) were studied, including 1,247 patients with recent-onset type 2 diabetes without glutamic acid decarboxylase autoantibodies (GADAs), 117 non–insulin-requiring patients with GADAs who had not received insulin therapy for at least 6 months after diagnosis (designated latent autoimmune diabetes of adults [LADA]), 288 type 1 diabetic patients, and 359 normal subjects.

**RESULTS** — Frequency of metabolic syndrome was significantly different in patients with type 1 diabetes (31.9%) and LADA (41.9%) ($P = 0.015$) and in both conditions was less frequent than in type 2 diabetic patients (88.8%) ($P < 0.0001$ for each). Eliminating glucose as a variable, the prevalence of metabolic syndrome was similar in patients with autoimmune diabetes (type 1 diabetes and/or LADA) (17.3%) and control subjects (23.7%) but remained more common in type 2 diabetic patients (47.8%) ($P = 0.001$ for all groups). In both type 1 diabetic patients and those with LADA, individual components of metabolic syndrome were similar but less common than in type 2 diabetic patients ($P < 0.0001$ for each).

**CONCLUSIONS** — The prevalence of metabolic syndrome is significantly higher in type 2 diabetic patients than in patients with LADA or adults with type 1 diabetes. Excluding glucose as a variable, metabolic syndrome is not more prevalent in patients with autoimmune diabetes than in control subjects. Metabolic syndrome is not a characteristic of autoimmune diabetes.

Type 1 diabetes is an autoimmune disease in which insulin deficiency results from immune-mediated destruction of insulin-secreting islet cells. The majority of patients with type 1 diabetes have autoantibodies in their peripheral blood, and these autoantibodies can predict the disease. Autoimmune diabetes, as characterized by these autoantibodies, such as glutamic acid decarboxylase autoantibodies (GADAs), is the most prevalent form of diabetes in children and also occurs in a proportion of patients who initially present with adult-onset non–insulin-requiring diabetes, also called latent adult-onset autoimmune diabetes (LADA) (1).

Because glucose disposal and blood glucose are determined by both insulin secretion and insulin action, it follows that insulin sensitivity could be important in the pathogenesis of autoimmune diabetes. Insulin sensitivity has not been studied in detail in autoimmune diabetes, although studies suggest that its loss may occur in established disease as well as in the pre-diabetic phase (2–5). Loss of insulin sensitivity is difficult to assess epidemiologically but is reflected in the cluster of metabolically related cardiovascular risk factors that together comprise the metabolic syndrome and include altered glucose levels, central obesity, dyslipidemia, and hypertension. Several groups, including the International Diabetes Federation (IDF) and the National Cholesterol Education Program (NCEP), with Adult Treatment Panel III (6), have proposed their own definitions for the metabolic syndrome.

LADA is clearly distinct from type 2 diabetes, in that LADA is associated with histocompatability (HLA) genes, diabetes-associated autoantibodies, reduced insulin secretion, no need for insulin therapy initially after diagnosis, and less prevalence of metabolic syndrome (7–9). The key question is whether LADA is distinct from type 1 diabetes (1,10,11), that is, whether LADA is one end of a rainbow of pathophysiological variations encompassing autoimmune diabetes with a frequency of metabolic syndrome similar to that of childhood-onset type 1 diabetes or whether LADA is a distinct form of autoimmune diabetes that resembles type 2 diabetes, showing evidence of insulin resistance with a high frequency of metabolic syndrome (1). Therefore, the aim of this study was to test whether individuals with type 2 diabetes and autoimmune diabetes (incorporating type 1 diabetes and LADA) have a higher frequency of metabolic syndrome than normal subjects, and our hypothesis was that they would.

## RESEARCH DESIGN AND METHODS

— The study design is cross-sectional and includes adult diabetic patients and control subjects (aged 30–70 years) from five European cities (London, Belfast, Lyon, Barcelona, and Rome) examined between 2004 and 2007. All patients came from five Euro-

pean hospital-based centers involved in Action LADA, a European Union–funded multicenter European study with the aim of identifying immune and clinical risk factors for adult-onset autoimmune diabetes (http://www.actionlada.org). Diabetes was designated according to standard criteria, and LADA was defined as patients aged 30–70 years with GADAs who did not require insulin treatment for at least 6 months after diagnosis (7,8). Type 1 diabetic patients and normal subjects fulfilling the inclusion criteria were ascertained consecutively from three of these five European centers (London, Barcelona, and Rome). The control subjects came from health centers in local communities.

Inclusion criteria were diagnosis of diabetes (with at least two fasting blood glucose measurements ≥7 mmol/l), time from diagnosis <5 years for all non–insulin-requiring diabetic patients, and age 30–70 years at examination. Patients came from Europe but with different ethnicity (91.7% Caucasian, 4.6% Middle Eastern, 1.4% Asian, 1.3% African, and 1.0% mixed race). Control subjects were individuals from local communities attending primary care centers for routine examination with age range and sex ratio similar to those of the patients and were all Caucasian. Exclusion criteria for both patients and control subjects were incomplete data set, current pregnancy, renal disease with a raised creatinine level or proteinuria, or acute illness at the time of testing; in addition, patients with non–insulin-requiring diabetes with duration of >5 years and control subjects with any clinical disease, therapy, or family history of autoimmune disease were excluded. Data on medication and risk factors were registered by the attending physician on the basis of the medical files. Serum and plasma samples were collected according to standard procedures and were stored at −80°C.

Each subject was tested locally for waist circumference and blood pressure. Blood pressure was measured at least twice in the sitting position. Lipids and lipoproteins (serum total and HDL cholesterol and triglycerides) were determined by standardized assays at each center. All initially non–insulin-requiring patients were tested for GADA in a central laboratory (London) as part of the European Union Action LADA program.

## Diagnostic criteria for metabolic syndrome

Metabolic syndrome was assessed according to the NCEP criteria (6) as follows: waist circumference >102 cm in men and >88 cm in women, triglycerides >1.70 mmol/l, HDL cholesterol <1.00 mmol/l in men and <1.30 mmol/l in women, blood pressure 130/85 mmHg or taking antihypertensive medication, and fasting glucose ≥6.1 mmol/l. We chose to identify all diabetic patients in this study as fulfilling the criteria for hyperglycemia. Three of five criteria were required for the diagnosis of metabolic syndrome. Because raised glucose is one criterion for metabolic syndrome and all diabetic patients, by definition, have raised glucose, we reanalyzed the data, excluding glucose as a variable.

## Antibody measurement

The radioimmunoprecipitation assay for GADAs uses human islet GAD65 cDNA with in vitro transcription and translation systems as described previously (12). All samples were centrally tested in London in duplicate, including positive and negative control standard sera. Each assay for GADA included in-house standard serum from a pre-diabetic individual serially diluted to an end point equivalent at 70 World Health Organization (WHO) units above which samples were scored positive. A separate positive serum sample (equivalent to the WHO standard of 200 WHO IU) was used as an in-house control to standardize each assay for unit calculation. In the Diabetes Antibody Standardization Program Antibody Workshop our assay had a sensitivity of 74% and specificity of 98% for GADAs (13). In the latest Diabetes Antibody Standardization Program workshop (2007) our assay had a sensitivity of 80% and specificity of 98% for GADAs (M.I.H., R.D.L., unpublished data). Positive samples were retested to confirm GADA positivity and reduce the false-positive rate. To compare the prevalence of metabolic syndrome with respect to the GADA titer in patients with LADA, we sought to divide them into two subgroups using a Q-Q plot of GADA-positive patients.

## Statistical analyses

The differences between groups were analyzed with a $\chi^2$ test or Fisher's exact test when appropriate. Quantitative variables were analyzed with a general linear model univariate, and a post hoc analysis was performed with a Bonferroni test; data are presented as means ± SD. A logistic regression analysis was performed to evaluate confounding by covariables, with adjustment for sex, age of onset, disease duration, and ethnicity to calculate the odds ratio (OR) for metabolic syndrome; three dummy variables were created to include three groups of patients with control subjects as a reference group. Data are presented as ORs with 95% CIs. Values for GADA levels, triglycerides, and HDL cholesterol were log-transformed to normalize distributions. All analyses were performed using SPSS for Windows (SPSS, Chicago, IL). $P < 0.05$ was considered statistically significant. Q-Q probability plots were used to analyze the distribution of GADA measurements for normality. Observed antibody values were plotted along the horizontal axis against expected normal values under normality on the vertical axis using Blom's proportion estimation formula. The study protocol is in accordance with the Declaration of Helsinki and was approved by local ethics committees in each study center. Informed written consent was obtained from all subjects before blood sampling.

**RESULTS** — Of the 2,011 subjects studied, for diabetic patients ($n = 1,652$), mean ± SD age was 52.7 ± 10.3 years, duration of diabetes was 5.2 ± 6.7 years, and 51.8% were men. For control subjects ($n = 359$), age was 53.5 ± 10.7 years and 51.0% were men. The demographics of the different groups are shown in Table 1. Of note, age was significantly lower in patients with type 1 diabetes (43.8 ± 9.8 years) than in those with LADA (49.7 ± 10.4 years) ($P < 0.0001$) and in both was lower than for type 2 diabetic patients (55.1 ± 10.1 years) ($P < 0.0001$). Clinical and biochemical features of each group are shown in Table 2.

The prevalence of metabolic syndrome, including hyperglycemia as a component, was 75.5% in all diabetic patients and 26.5% in control subjects ($P < 0.0001$). Metabolic syndrome was detected in significantly more patients with type 1 diabetes (31.9%) and LADA (41.9%) than in control subjects ($P = 0.006$). Referring to control subjects, the ORs (95% CI) for metabolic syndrome are as follows: for type 2 diabetes 22.5 (15–33.7) ($P < 0.0001$); for LADA 2.2 (1.2–3.6) ($P < 0.004$); and for type 1 diabetes 1.1 (0.7–1.9) ($P = 0.6$). There was a significant difference in the OR between type 1 diabetes and LADA for metabolic syn-

**Table 1—Demographics of the groups**

| | Normal | Type 1 diabetes | LADA | Type 2 diabetes |
|---|---|---|---|---|
| n | 359 | 288 | 117 | 1247 |
| Female sex (%) | 176 (49) | 156 (54.2) | 56 (47.8) | 665 (53.3) |
| Age (years) | 53.6 ± 10.7* | 43.8 ± 9.8* | 49.4 ± 10.2* | 55.1 ± 9.1† |
| Age of onset (years) | — | 25.7 ± 11.7* | 47.1 ± 10.4* | 52.7 ± 9.2* |
| Disease duration (years) | — | 18.2 ± 11.7‡ | 2.7 ± 1.8‡ | 2.4 ± 1.8‡ |

Data are means ± SD unless otherwise indicated. *$P < 0.0001$: type 1 diabetes versus LADA and LADA versus type 2 diabetes and controls. †$P = 0.043$: type 2 diabetes versus controls. ‡$P < 0.0001$: type 1 diabetes versus LADA and type 2 diabetes.

drome, even after correction for age, duration of disease, sex, and ethnicity: 3.2 (1.2–8.3) ($P = 0.015$). The prevalence of metabolic syndrome was higher in type 2 diabetic patients (88.8%) than in patients with either LADA (41.9%) or type 1 diabetes (31.6%) ($P < 0.0001$ for both comparisons). No differences were seen in sex for metabolic syndrome (50% men vs. 50% women). The risk of metabolic syndrome increases with age: 1.05 (1.04–1.06) per year ($P < 0.0001$).

When glucose was excluded as a variable, metabolic syndrome was not more prevalent in patients with autoimmune diabetes (type 1 diabetes and LADA) (17.3%) than in control subjects (23.7%) but remained more prevalent in type 2 diabetic patients (47.8%) ($P = 0.001$ for all groups). Metabolic syndrome was less prevalent in patients with type 1 diabetes (16.9%) than in those with LADA (25.0%) or control subjects (23.7%) ($P = 0.04$), and the prevalence was similar in the two latter groups ($P = 0.7$). For control subjects the ORs (95% CI) were as follows: for type 2 diabetes 2.4 (1.6–3.6) ($P < 0.0001$); for LADA 0.9 (0.50–1.60) ($P = 0.69$); and for type 1 diabetes 1.1 (0.39–1.12) ($P = 0.60$). The frequency of metabolic syndrome for all groups was still similar in men (53.1%) and women (46.9%) ($P = 0.45$). The risk of metabolic syndrome still increased with age: 1.02 (1.01–1.03) per year ($P < 0.0001$). It follows that factors associated with meta-

bolic syndrome include diabetes and older age and, when glucose is excluded as a trait, type 2 diabetes and older age.

Of the individual components of the metabolic syndrome, after adjustment for age of onset, duration of disease, sex, and ethnicity, waist circumference was similar in patients with type 1 diabetes and LADA ($P = 0.44$) but was lower in each of these groups than in patients with type 2 diabetes ($P < 0.0001$ for both comparisons), systolic and diastolic blood pressures were similar in patients with type 1 diabetes and LADA ($P = 0.28$ and $P = 0.49$, respectively) but was lower in each of these groups than in patients with type 2 diabetes ($P < 0.0001$), triglycerides were similar in patients with type 1 diabetes and LADA ($P = 0.63$) but lower in each of these groups than in patients with type 2 diabetes ($P < 0.0001$), and HDL cholesterol was similar in patients with type 1 diabetes and LADA ($P = 0.40$) and in both groups was higher than in patients with type 2 diabetes ($P < 0.0001$). Waist circumference in the combined diabetes groups ($n = 1,652$) was directly associated with age at sampling ($r = 0.28$; $P < 0.0001$) and inversely related with disease duration ($r = -0.28$; $P < 0.0001$). Of the individual components, increases in waist circumference ($r = 0.16$; $P < 0.0001$) and systolic blood pressure ($r = 0.29$; $P < 0.0001$) and elevated triglycerides ($r = 0.13$; $P < 0.0001$) but not diastolic blood pressure ($r = 0.03$; $P = 0.26$) were more

common with increasing age, whereas HDL cholesterol ($r = -0.09$; $P < 0.008$) decreased with age.

A Q-Q plot of GADA-positive patients was performed to seek distinct populations, and we identified an inflection point corresponding to 200 WHO IU consistent with two modes (data not shown). Further, a plot of the GADA titer according to patient frequency revealed a possible bimodality, and the lowest value between the two modes was at a GADA titer of 200 WHO IU (data not shown). Therefore, we arbitrarily analyzed the metabolic syndrome according to GADA positivity in those with a GADA titer of >200 or <200 WHO IU and found that it was similar in LADA patients with high (>200 IU) ($n = 39$) and low (70–200 IU) ($n = 78$) GADA titers (47.3 and 40.3%, respectively) even after correction for age, sex, duration of disease, and ethnicity ($P = 0.37$, 95% CI 0.29–1.6).

The frequency of features of metabolic syndrome formed a hierarchy that was similar in all the groups, irrespective of the presence or type of diabetes, such that high blood pressure > elevated waist circumference > high triglycerides > low HDL cholesterol. Among those patients with the metabolic syndrome, the most frequent features of its components are shown in Table 3. The cluster of hyperglycemia, increased waist circumference, and high blood pressure was seen in 62.1% of those with the metabolic syndrome, whereas hyperglycemia, hypertension, high triglycerides, and low HDL cholesterol were seen in 17.9%.

**CONCLUSIONS** — These observations indicate that the metabolic syndrome is a frequent finding in autoimmune diabetes but is not more frequent in autoimmune diabetes than in normal subjects when glucose is excluded as a risk factor. In contrast, metabolic syndrome is far more prevalent in type 2 diabetes, even when glucose is excluded as a variable. Whether glucose was or was not used as a variable, we found that individual components of the metabolic syndrome in both patients with type 1 diabetes and those with LADA were similar but in each group were less than those seen in type 2 diabetic patients. It follows that there is no evidence from this data set that autoimmune diabetes is distinct in terms of prevalence of metabolic syndrome from that in normal subjects and the hypothesis that it would be distinct is rejected. Nevertheless, metabolic syndrome was more prevalent in patients

**Table 2—Clinical and biochemical characteristics of each group of subjects**

| | Normal subjects | Type 1 diabetes | LADA | Type 2 diabetes |
|---|---|---|---|---|
| Waist circumference (cm) | 93.7 ± 17 | 89.6 ± 14.4 | 93 ± 15.5 | 107.2 ± 13.8 |
| Systolic blood pressure (mmHg) | 130.6 ± 14.6 | 127.1 ± 14.8 | 126.9 ± 16.9 | 141.3 ± 17.4 |
| Triglycerides (mmol/l) | 1.7 ± 0.8 | 1.3 ± 0.7 | 1.6 ± 1.4 | 2 ± 1.5 |
| HDL cholesterol (mmol/l) | 1.5 ± 0.4 | 1.6 ± 0.5 | 1.5 ± 0.5 | 1.3 ± 0.4 |

Data are means ± SD.

**Table 3—***Percentage of subjects with values over cutoff for each component of metabolic syndrome*

|  | Normal subjects | Type 1 diabetes | LADA | Type 2 diabetes |
|---|---|---|---|---|
| *n* | 359 | 288 | 117 | 1,247 |
| Glucose | 6.7 | 100 | 100 | 100 |
| Waist circumference | 43.7 | 25.7 | 35.9 | 82.8 |
| Systolic blood pressure | 65.9 | 50.7 | 49.6 | 86.7 |
| Triglycerides | 39.6 | 23.6 | 35.8 | 49.8 |
| HDL cholesterol | 21.2 | 17 | 29 | 36.1 |

Patients with type 2 diabetes have a higher frequency of increased waist circumference and systolic blood pressure. Patients with autoimmune diabetes (type 1 diabetes and LADA) tend to resemble normal subjects for all features apart from increased blood glucose (although a fraction of normal subjects had impaired fasting glucose).

with LADA than in those with type 1 diabetes when glucose was included as a variable.

Glucose is a debatable component of the metabolic syndrome and was introduced for assessing type 2 diabetes and not type 1 autoimmune diabetes (14). When glucose was excluded, the prevalence of metabolic syndrome in patients with autoimmune diabetes was not greater than that in normal subjects. Therefore, there is no evidence to suggest that autoimmune diabetes is due to decreased insulin sensitivity; instead, decreased insulin sensitivity might predispose to an earlier time of diagnosis. Such decreased insulin sensitivity could explain why age, overweight, and physical inactivity are as strongly predictive of LADA as they are of type 2 diabetes (15,16). These present observations indicate that metabolic syndrome is as common in adults with autoimmune diabetes as it is in normal subjects. Thus, agents such as metformin and other insulin sensitizers may be beneficial in autoimmune diabetes, as they are in type 2 diabetes, in line with recent studies indicating that metformin is efficacious in type 1 diabetes (17).

Of the three current criteria for metabolic syndrome (IDF, NCEP, and WHO), we used the NCEP criteria because they are more appropriate to apply here to populations of variable geographical origin rather than the IDF criteria, for simplicity, and the WHO criteria, which include insulin resistance and microalbuminuria (6). Although it is possible that metabolic syndrome should be defined differently in autoimmune diabetes, including type 1 diabetes and LADA, the hierarchy of features associated with metabolic syndrome was similar to that found in type 2 diabetic patients and control subjects. Nevertheless, the metabolic syndrome was not originally introduced to identify a feature of autoimmune diabetes

but to capture the clustering of a group of continuous variables associated with cardiovascular risk. That cluster has subsequently been extended to include measures of endothelial dysfunction and low-grade inflammation, but it remains unclear whether these new parameters are also features of autoimmune diabetes; for example, type 2 diabetes is associated with increased levels of proinflammatory serum cytokines and acute-phase proteins, especially in association with obesity, whereas in type 1 diabetes such inflammatory changes are mild or nonexistent (18). Patients with LADA have not been consistently found to exhibit the systemic low-grade inflammation previously identified in type 2 diabetic patients (18). Thus, it is reasonable to conclude that autoimmune diabetes, whether type 1 diabetes or LADA, differs from type 2 diabetes with respect to systemic low-grade inflammation, as it does with metabolic syndrome.

Previous studies of metabolic syndrome in LADA have confirmed that, although it is prevalent, it is less prevalent than in type 2 diabetes (19,20). There are only two previous studies comparing LADA with type 1 diabetes, each suggesting a tendency for LADA to have more features of the metabolic syndrome, but control subjects were not included; each study was very small with a combined total of 94 patients with LADA and 112 type 1 diabetic patients, and one of them used highly selected patients with LADA (9,21). Large studies of type 1 diabetes have identified a prevalence of metabolic syndrome of 39% in Finnish patients, which was approximately three times the separately observed prevalence in nondiabetic Finnish subjects (22) and higher than the frequency in American patients with type 1 diabetes (22%) (23). However, in the latter study frequency of metabolic syndrome increased from 14.6 to

36.1% after a duration of diabetes of 9 years (23). It follows that there is a dynamic in the frequency of metabolic syndrome in autoimmune diabetes, whether type 1 diabetes or LADA, which must be considered in comparing the groups. Therefore, the disparity in the prevalence of metabolic syndrome between the Finnish and American studies and our own European study probably reflects differences in population characteristics including duration of diabetes, renal function, intensive insulin therapy, male sex, and age, all of which have been independently associated with metabolic syndrome.

There is some limited evidence, other than the clinical phenotype, to support the contention that LADA is an intermediate form of diabetes between type 1 diabetes and type 2 diabetes. LADA, albeit defined as GADA positivity irrespective of therapy, was reported to be associated with the CT and TT genotypes of the *TCFL2* gene and, therefore, apparently shares genetic features with type 2 diabetes (24). However, the high false-positive rate of the GADA assay used in that study raises issues regarding the validity of the observation. We limited this potential error by repeating GADA assays in GADA-positive subjects, thereby reducing the risk of false positivity to <0.2%, much less than the proportion of patients with LADA. The error from not testing other diabetes-associated autoantibodies is probably small, given that 94% of patients with LADA sampled from this cohort were detected by GADA testing alone (M.I.H., R.D.L., unpublished data). The proposal that the metabolic syndrome is more prevalent in patients with LADA who also have a low GADA titer compared with those with an arbitrarily selected high titer of GADA was not confirmed in this present study using a Q-Q plot to identify two apparently distinct GADA-positive distributions (20). However, there is substantial variation between laboratories with respect to threshold GADA titers defining a positive result, and caution should be exercised in using such thresholds.

Thus, metabolic differences between LADA and type 1 diabetes may not be categorical but part of a continuum, implying that LADA is one end of a rainbow of a pathophysiological variation encompassing autoimmune diabetes (1). If we accept the fact that metabolic syndrome is a surrogate marker for insulin resistance, there is now evidence that patients with LADA are more insulin resistant than adult type 1 diabetic patients but not

when glucose is excluded as a variable, when insulin resistance in both is similar to that in normal subjects. This conclusion is important, as it implies that autoimmune diabetes, whether type 1 diabetes or LADA, can be identified by diabetes-associated autoantibodies, e.g., GADAs, as a categorical trait, irrespective of individual components of the metabolic syndrome or the need for insulin treatment. Indeed, we have previously suggested that insulin treatment is an insubstantial feature to diagnose LADA because it is subject to local issues such as medical practice and context, including availability of GADA results (25). Thus, the role of insulin resistance in autoimmune diabetes may be limited, and there is no characteristic clinical phenotype of adult-onset autoimmune diabetes; specifically, neither forms of autoimmune diabetes showed an increased frequency of metabolic syndrome in striking contrast with type 2 diabetes.

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