Intensification of therapy and no increase in body mass index with longer disease duration in type 2 diabetes mellitus (ZODIAC-5)

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**Background.** Decreased insulin sensitivity and β-cell failure are the two key components in the pathogenesis of type 2 diabetes mellitus (T2DM). Secondary treatment failure is often attributed to the development of obesity-related insulin resistance in combination with continued loss of β-cell function.

**Objective.** Assess metabolic control, body mass index (BMI) and treatment in relationship to diabetes duration to study these mechanisms.

**Methods.** Cross-sectional study of 7875 patients with T2DM in primary care in The Netherlands. Clinical data and laboratory results were obtained for the 2005 annual visit. Patients were grouped according to diabetes duration in 2-year intervals. Each step in the traditional treatment sequence was considered as a sign of progression of β-cell failure.

**Results.** Complete data regarding duration and treatment were available for 6850 patients (87%). After the initial years following diagnosis, treatment with diet alone decreases and oral hypoglycaemic agents (OHA) are prescribed to an increasing percentage of patients. Treatment with OHA diminishes after approximately 10 years following diagnosis and treatment with insulin increases until approximately two-thirds of patients with diabetes duration of more than 20 years are being treated with insulin. BMI does not increase with longer disease duration.

**Conclusion.** The concept of β-cell failure as the primary determinant of the chronic progression of T2DM is supported by these results, whereas a deterioration of obesity-related insulin sensitivity as indicator is not supported.

**Keywords.** β-cell failure, insulin resistance, primary health care, therapy, type 2 diabetes mellitus.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the risk factors compounding a person’s total cardiovascular risk. Decreased insulin sensitivity and β-cell failure are the two key components in the pathogenesis of T2DM. The progressive nature of this disease necessitates the intensification of therapy over time. The secondary failure seen in patients with T2DM is often attributed to the development of obesity-related insulin resistance in combination with a continued loss of β-cell function.

We performed a cross-sectional evaluation to assess metabolic control and treatment in relationship to diabetes duration in T2DM in a large cohort of primary care patients.

**Methods**

The ZODIAC (Zwolle Outpatient Diabetes project Integrating Available Care) study investigates the effects of a shared care project for T2DM. Patients with cognitive disability or terminal diseases were excluded.
National guidelines for the treatment of diabetes were implemented. The study is described in detail elsewhere.

In the Netherlands, T2DM is predominantly treated in primary care. Primary care patients with T2DM who were participating in the shared care project were eligible for this study. Clinical data (age, sex, body mass index (BMI), blood pressure (BP), disease duration, current medication) and laboratory results were obtained for the 2005 annual visit from the Diabetic Electronic Monitoring System database. HbA1c was measured with a Primus Ultra2 using high-performance liquid chromatography. Other laboratory measurements were obtained according to standard procedures of the Isala Clinics.

Each step in the traditional treatment sequence (i.e. diet, oral hypoglycaemic agents (OHA), insulin treatment) was considered as a sign of progression of β-cell failure. Patients were grouped according to disease duration in 2-year intervals. One-way analysis of variance and chi-square tests were used to test differences. We used SPSS software v12.0.1 (SPSS, Chicago, IL) for statistical analyses. Statistical significance was taken at the 0.05 (two-tailed) level.

Results

In 2005, 7875 patients (47% male) with T2DM were being treated by 154 GPs as part of the shared care project. Mean age, BMI, HbA1c, systolic BP, estimated glomerular filtration rate (eGFR) and total cholesterol were 68.2 ± 11.7 years, 29.6 ± 5.1 kg/m², 6.8 ± 1.0%, 144 ± 19 mmHg, 74 ± 28 ml/min and 4.7 ± 1.0 mmol/l, respectively (mean ± SD). Median (P25–P75) diabetes duration was 5.0 (2.4–8.5) years.

In 2005, 1542 (19.6%) patients were being treated with diet alone (mean age 66.7 ± 11.3 years, mean HbA1c 6.2 ± 0.7%), 4989 (63.4%) patients were being treated with OHA (mean age 68.0 ± 11.8 years, mean HbA1c 6.8 ± 1.0%) and 1344 (17.1%) patients were being treated with insulin (mean age 70.5 ± 11.4 years, mean HbA1c 7.4 ± 1.0%) (P < 0.001 for age and HbA1c among all three groups). HbA1c was >7.0% in 8.7% of patients treated with diet alone, in 34.5% of patients treated with OHA and in 65.9% of patients treated with insulin (P < 0.001).

With respect to disease duration and treatment regimen, 87.0% (n = 6850, 47.1% male) of patients with complete data sets could be analysed. There were no significant differences in age, BMI, total cholesterol, and eGFR between patients that were included in this analysis and those that were not (n = 1025).

Figure 1 shows BMI (bars) and patient percentages (lines) per therapy regimen versus disease duration. BMI decreases with longer duration [analysis of variance (ANOVA), P < 0.001]. However, the correlation coefficient of diabetes duration and BMI is small (r = –0.1, P < 0.01) and further decreases when controlling for age. After the initial years following diagnosis, the proportions of patient treated with diet alone decreases from 24% at 2–4 years to 4% at >10 years of disease duration. Treatment with OHA diminishes after approximately 8–10 years following diagnosis (72%, 67% and 33% of patients at 2–4 years, 8–10 years and >20 years of disease duration, respectively), and treatment with insulin increases until approximately two-thirds of patients are being treated with insulin (5%, 37% and 64% of patients at 2–4 years, 10–12 years and >20 years of disease duration, respectively).

Age and HbA1c increase with longer disease duration (data not shown; ANOVA, P < 0.001).
Discussion

These results confirm that to reach adequate metabolic control, treatment needs to be intensified as disease duration increases.

The concept of β-cell failure as the primary determinant of the chronic progression of T2DM is supported by these results; whereas deterioration of obesity-related insulin sensitivity and obesity-related impaired β-cell function by adipocyte-derived cytokines is not.8

In normal daily practice, therapy intensification may be necessary due to various causes. Our results suggest that with advancing disease duration, especially in subjects with a stable body weight, progressive β-cell failure should be taken into account. When therapy options directed towards improving insulin sensitivity fail (e.g. altering lifestyle or metformin), insulin could be considered as an early option. Such therapy intensification should then be seen as an adequate compensation for progressive β-cell function deterioration.

A limitation of this study is the use of an indirect marker for β-cell failure instead of a direct measure. The cross-sectional design is a potential limitation as it does not allow to study cause and effect relations; however, this design avoids the possibly confounding effects of changing guidelines and/or treatment protocols. The possibility remains that obese patients died earlier than less obese patients; however there is conflicting evidence on this subject.9 Furthermore, it is a very heterogeneous population and we cannot exclude influence of treatment preferences and other potential confounders or effect modifications.

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Declaration

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Conflicts of interest: None.

References

6 Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. Diabetes Care 2001; 24: 89–94.