Early onset type 2 diabetes mellitus: a harbinger for complications in later years—clinical observation from a secondary care cohort

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Summary

Background: Little is known about the complication burden in later years among early onset type 2 diabetes mellitus (T2DM).

Aim: To determine the magnitude of diabetes complications and adequacy of risk factor management and to test the hypothesis that diabetes duration is an important contributing factor to these complications.

Design: A cross-sectional study of secondary care diabetes population.

Methods: Data on glycaemic control, cardiovascular risk factors (overweight/obesity, hypertension, dyslipidaemia), cardiovascular disease (CVD) and microvascular complications among those diagnosed before (early onset) and after (later onset) 40 years of age at different diabetes durations (<10, 10–20 and >20 years) were analysed.

Results: A total of 2733 subjects were identified, of which 527 had diabetes diagnosed below the age of 40 years. By the sixth decade of life, early onset cohort experienced high complication burden (CVD: 37.2%, retinopathy: 59.3% and neuropathy: 53.1%). Complication prevalence increased with diabetes duration but the increment rate was greater among early onset cohort. Compared with those diagnosed after 40, early onset cohort experienced similar burden of microvascular complications ~13–20 years earlier. Diabetes duration was a significant predictor for microvascular and CVD complications. Prevalence of CVD risk factors was high (~80–93%) regardless of the age of diagnosis and diabetes duration. Early onset subjects were more likely to have poorer glucose control (~70–78%), untreated hypertension (26.3%) and a substantial number did not receive statin treatment for primary prevention (34.8%).

Discussion: Early onset T2DM subjects are at substantial risk of developing diabetes complications in later years but at an earlier stage than later onset cohort and prolonged exposure to adverse diabetic milieu is an important contributing factor. Management of risk factors for diabetes complications was inadequate among early onset subjects.

Introduction

The global burden of type 2 diabetes mellitus (T2DM) is significant and rising, with most of the increase occurring in the last two decades. The worldwide prevalence of diabetes in adults is expected to increase from 5% to 6.2% between 2003 and 2025.¹ While most of the rise in the prevalence of T2DM occurs in middle-aged and elderly, it is becoming more common among younger patients, including children and adolescents. The fall in age of onset of T2DM is driven by increasing obesity in the younger age group. This is supported by the observation of an inverse relationship between obesity and age of diagnosis of T2DM.² Of concern is the fact that obesity has
increased by 70% in adults aged between 30 and 39 years, thus, making young adults the fastest growing group for obesity and T2DM.\footnote{We have previously demonstrated that despite the young age, early onset cohort possessed adverse cardiovascular risk profile characterized by multiple risk factor clustering (obesity, hypertension, dyslipidaemia) and suboptimal glycaemic control\textsuperscript{4} which mirrored the findings from other studies.\textsuperscript{5,6}} Given the potential long duration of exposure to this adverse milieu, it is plausible that these young subjects are at risk of developing significant diabetes-related complications at later stages of their lives. Another possibility is that early diagnosis of T2DM in young subjects confers an inherently aggressive phenotype to develop complications, more so than the later onset cohort.\textsuperscript{7} At present, no study has examined long-term outcomes as a function of age of diagnosis of T2DM in the UK. This knowledge will be immensely invaluable to support the argument that intensive clinical management is mandatory in these young diabetics to prevent or reduce future development of complications and the associated morbidity and mortality.

This study builds on our previous work and is designed to bridge the existing knowledge gap by addressing these fundamental clinical questions: (i) to determine whether early onset T2DM subjects are at risk of developing future diabetes-related complications; (ii) to determine the magnitude of diabetes-related complications compared with later onset cohort of similar disease duration; (iii) to determine whether diabetes duration and/or lower age of diagnosis is a contributing factor to complication development in early and later onset cohort; and (iv) to determine the adequacy of risk factor management among early vs. later onset cohort.

## Methods

This was a cross-sectional study using secondary care T2DM population and subjects were identified from hospital diabetes register. This electronic diabetes database records clinical details of all subjects with types 1 and 2 diabetes who attend clinics at Northern General Hospital and Royal Hallamshire Hospital for their clinical care. The clinical data were routinely entered into this database each time the diabetic subjects were seen at these clinics. All data relevant to this study were collected in 2008 as the part of the annual audit and service evaluation process within the diabetes department. Those known to have latent autoimmune diabetes in adult (LADA), maturity onset diabetes of the young (MODY), gestational diabetes and secondary diabetes were excluded. Early and later onset T2DM refer to those whose diabetes was diagnosed below and above the age of 40 year, respectively, as defined by the NICE guideline for T2DM\textsuperscript{8} and Joint British Societies-2 guideline.\textsuperscript{9} For each patient, data on clinical characteristics, prevalence of microvascular disease (retinopathy and neuropathy) and cardiovascular disease (CVD), which included ischaemic heart disease, peripheral vascular disease and stroke, were collected. Data on microalbuminuria were not available as this test was not routinely performed in the management of T2DM in Sheffield. To assess the impact of diabetes duration on complication outcomes, early and later onset cohort were categorized into three different diabetes durations, namely, <10, 10–20 and >20 years.

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) for Windows (SAS Institute, Cary, NC, USA). Continuous data were expressed as mean and standard deviation (SD), while categorical data were expressed as absolute subject number and percentage. The normality of continuous data distribution was tested to determine the appropriate method for parametric or non-parametric statistical analysis. Mann–Whitney U-test and chi-squared ($\chi^2$) test were used to compare variables between two groups. The $\chi^2$-value for the trend was used to determine the significance of trends in frequency across different groups. Logistic regression was used to determine the significance of diabetes duration and age of diabetes onset as a predictor for the development of microvascular and CVD complications. P < 0.05 is considered significant.

## Results

A total of 2733 subjects were included in this study, of which 527 had diabetes diagnosed below the age of 40 years. The clinical characteristics of the study subjects as stratified by diabetes duration are shown in Table 1. The mean age of diagnosis was \( \sim \)32 years and between 50 and 55 years among the early and later onset cohort, respectively. Irrespective of the age of diagnosis and diabetes duration, majority (\( \sim \)82–93\%) of subjects possessed multiple CVD risk factors (overweight/obese, hypertension, dyslipidaemia).

The relationship between diabetes duration and microvascular and CVD complications is shown in Table 2 and Figure 1, while Table 3 shows the prevalence of diabetes complications in relation to mean current age. Among those with shortest diabetes duration (<10 years), the prevalence of complications was higher in later onset cohort.
Increasing diabetes duration was associated with higher prevalence of complications irrespective of age of diagnosis. Using diabetes duration <10 years as reference, the rate of increment for microvascular and CVD complications with increasing diabetes duration was greater for those diagnosed below the age of 40 years (Figure 1) to the extent that comparable magnitude of microvascular complications occurred at an earlier age in early onset cohort (Table 3). This occurred ∼13–20 years earlier than later onset cohort (retinopathy/neuropathy prevalence of 30–35%; early vs. later onset, 49.7 vs. 70.4 years and retinopathy/neuropathy prevalence of 50–60%; early vs. later onset, 62.4 vs. 75.5 years). At a similar current age (∼63 years), the prevalence of CVD for early onset cohort with long diabetes duration (mean: 28.7 years) exceeded those of later onset cohort with short diabetes duration (mean: 6.5 years; early vs. later onset; 37.2 vs. 31.1%).

The question as to whether diabetes duration and/or lower age of diagnosis are predictive factors for the development of diabetes complications among early and later onset cohort is examined by logistic regression analysis and the findings are shown in Table 4. Clearly, diabetes duration was a significant predictor of microvascular and CVD complications for early and later onset cohort and this would be in agreement with the observation summarized in Table 2. In contrast, lower age of diagnosis did not appear to be an important factor. Among early onset cohort, lower age of diagnosis was not associated with the development of complications (CVD: odds ratio (OR) 1.05, P = 0.023; retinopathy: OR 0.99,
Figure 1. Magnitude of increment in diabetes-related complications.

Table 3  Mean current age and prevalence of diabetes-related complications

<table>
<thead>
<tr>
<th>Diabetes duration (years)</th>
<th>Age of diagnosis &lt;40 years</th>
<th>Age of diagnosis &gt;40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10</td>
<td>10–20</td>
</tr>
<tr>
<td>Mean current age (years)</td>
<td>39.8</td>
<td>49.7</td>
</tr>
<tr>
<td>CVD (%)</td>
<td>8.4</td>
<td>18.7</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>4.4</td>
<td>35.5</td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>12.3</td>
<td>32.9</td>
</tr>
</tbody>
</table>
Table 4  Logistic regression analysis of diabetes duration and age of diabetes onset as predictor for diabetes-related complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Age of diagnosis &lt;40 years</th>
<th>Age of diagnosis &gt;40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>1.09 (1.06–1.11)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>1.13 (1.11–1.16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1.08 (1.06–1.10)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age of diabetes onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>1.05 (1.01–1.10)</td>
<td>0.023</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0.99 (0.96–1.03)</td>
<td>0.8</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1.07 (1.02–1.09)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Table 5  Management of risk factors for diabetes-related complications

<table>
<thead>
<tr>
<th>CVD risk management</th>
<th>Age diagnosis &lt;40 years</th>
<th>Age diagnosis &gt;40 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of CVD + at least two risk factors without statin treatment (%)</td>
<td>109 (34.8)</td>
<td>414 (39.0)</td>
<td>0.295</td>
</tr>
<tr>
<td>No. of CVD + hypertension without anti-hypertensive treatment (%)</td>
<td>86 (26.3)</td>
<td>185 (16.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Glycaemic control

*Mean HbA1c (%)*

<table>
<thead>
<tr>
<th></th>
<th>Diabetes duration &lt;10 years</th>
<th>Diabetes duration &gt;20 years</th>
<th>Proportion with HbA1c &gt;7.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.9 (2.0)</td>
<td>8.3 (1.9)</td>
<td>172 (71.4)</td>
</tr>
<tr>
<td></td>
<td>9.2 (2.0)</td>
<td>8.5 (1.7)</td>
<td>503 (58.9)</td>
</tr>
<tr>
<td></td>
<td>8.9 (1.7)</td>
<td>8.3 (1.3)</td>
<td>132 (77.4)</td>
</tr>
<tr>
<td></td>
<td>139 (77.9)</td>
<td>199 (66.3)</td>
<td>199 (66.3)</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (±SD) unless noted otherwise.

P = 0.80; neuropathy: OR 1.07, P = 0.004]. Except for retinopathy (OR 0.97, P = 0.04), lower age of diagnosis was also not significantly associated with diabetes complications in later onset cohort (CVD: OR 1.03, P = 0.001; neuropathy: OR 0.99, P = 0.89). This finding is in contrast with those of diabetes duration which has been shown to be a consistent significant predictive factor regardless of the nature of complications in early and later onset cohort. Based on this pattern of observations, it is unlikely that lower age of diagnosis is a significant predictor of diabetes complications, particularly among those whose diabetes were diagnosed at a young age.

The adequacy of glycaemic control and CVD primary prevention management is shown in Table 5. Early onset T2DM cohort had significantly poorer glycaemic control across all diabetes durations and higher proportion of untreated hypertension compared with those diagnosed later. Despite having at least two co-existing cardiovascular risk factors (obesity, hypertension, dyslipidaemia), a substantial number of early and later onset subjects did not receive statin treatment as recommended by the UK guidelines.8,9

Discussion

The principal clinical concern with T2DM subjects diagnosed at a young age is the potential development of clinically significant complications and the associated morbidity and mortality at an earlier stage of life than those diagnosed later. Various studies have provided definitive evidence for unfavourable glycaemic and cardiovascular risk profile in young T2DM, but the crucial link to subsequent occurrence and magnitude of micro- and macrovascular complications is lacking. In this study, we have addressed this knowledge gap for the first time in a UK population. We demonstrated that early onset T2DM is not a benign condition, but a high-risk phenotype to develop significant future
microvascular and CVD complications at a younger age than later onset cohort. Exposure to adverse diabetic milieu in the early stages of the natural history of T2DM is an important contributing factor to this phenomenon. Our novel findings are clinically relevant as it can potentially change the misperception of the risk status of early onset T2DM subjects and positively influence its management, particularly the intensiveness of risk factor and glycaemic intervention.

Although the absolute risk for diabetes complications is small among early onset subjects with short diabetes duration as manifested by the low complication prevalence, these subjects, however, have an extremely high lifetime risk by virtue of the long disease duration and exposure to the hyperglycaemic environment and its associated atherogenic risk factors. Our findings serve to illustrate the importance of understanding the fundamental conceptual difference between absolute and lifetime risk in clinical practice. Comparable complication burden occurred at an earlier stage for early onset cohort indicating that these subjects are more likely to experience higher complication rate than later onset cohort at similar chronological age. Obesity is known to accentuate the lifetime risk for CVD in diabetes.\(^\text{10}\) In our study, vast majority (>90%) of early onset subjects with short diabetes duration were either overweight or obese. It is evident from our findings that current age is a poor barometer to gauge the risk of developing future complications in young T2DM subjects.

Recent evidence is accumulating to support the concept of cardiometabolic memory where intensive management of glycaemia and CVD risk factors during early stages of T2DM can lead to subsequent reduction in micro- and macrovascular complications much later in the course of disease.\(^\text{11,12}\) Translating this concept into clinical practice is of utmost importance in the management of those whose diabetes is diagnosed at a young age given their adverse baseline clinical characteristics and high complication burden in the future. Worryingly, our observation indicates that risk factor intervention is less rigorous for these subjects including those with short diabetes duration. Contributing factors include misconception of young diabetics as being low risk, lack of robust randomized controlled trial evidence and reluctance to expose these subjects to potentially lifelong treatments.\(^\text{13}\)

It is known that a significant proportion of people with diabetes remain undetected.\(^\text{14}\) Screening for T2DM can identify patients at an earlier stage of the disease who might benefit from intensive diabetes control and treatment of adverse risk factors. In the UK, the Department of Health recently introduced the National Health Service Health Check programme for individuals aged between 40 and 74 years which involved checking blood glucose to detect new cases of diabetes as well as screening for risk factors predisposing to CVD.\(^\text{15}\) Since diabetogenic and atherogenic risk factors are present in high-risk young adults, it can be argued that screening should also include those aged <40 years. This debate is supported by the findings of a recent study using the ADDITION Cambridge cohort to assess the magnitude of CVD risk reduction achieved through early intensive pharmacological intervention in T2DM subjects aged >40 years diagnosed through screening.\(^\text{16}\) Majority of the screen-detected subjects (mean age of diagnosis: ~62 years) were overweight or obese, hypertensive and dyslipidaemic, the prevalence of these risk factors were similar to our early onset cohort (mean age of diagnosis: ~32 years). Failure to detect T2DM in the young represents a missed opportunity to improve the health of this vulnerable but important segment of the population.

There is an evidence to suggest that early onset diabetes is associated with an increased risk for complications compared with later onset diabetes\(^\text{6}\) and that the development and progression of complications might be more rapid in early onset disease.\(^\text{7}\) Various hypotheses have been proposed including longer lifetime exposure to adverse diabetic milieu and early onset T2DM as an inherently more aggressive metabolic phenotype. Our findings support the former hypothesis and this is in agreement with the observations from other studies.\(^\text{17,18}\) We did not find any consistent association between lower age of diabetes onset with greater diabetes complications, particularly among early onset subjects. The strength of our analysis included the incorporation of a range of matched diabetes durations up to >20 years which allowed sufficient time for complications to occur particularly for CVD. Nevertheless, there are evidence to support the hypothesis that early onset diabetes may be an inherently aggressive phenotype. A recent study demonstrated the prevalence and severity of retinopathy was higher in early onset cohort compared with later onset cohort of similar disease duration.\(^\text{19}\) Other studies examined the effect of physical activity on insulin resistance and serum CVD risk markers and after 3 months of exercise, there was no improvement in these parameters.\(^\text{20,21}\) From the clinical perspective, all these evidence strengthen the conviction that prevention and early detection of diabetes among the young should be a priority in public health strategy.
There are limitations to this study. First, our observation may not be extrapolated to the majority of T2DM subjects whose care is delivered in the community as this study cohort is based on a secondary care population. While it could be argued that early onset subjects with worse glycaemic and CVD risk profile are preferentially referred to hospital clinics, our observation is consistent with those of large population-based epidemiological studies. Second, the cross-sectional nature of this study precludes the opportunity to determine the absolute levels of risk factors measured in early onset subjects that predict diabetes-related complications in later years. Third, the totality of microvascular complication burden could not be determined as there was no complete data on microalbuminuria. Finally, there was no data on mortality and end-stage complications such as blindness, dialysis and amputations.

In conclusion, T2DM is a high-risk condition regardless of age of onset. Significant risks reside in the future development of premature micro- and macrovascular complications among those who were diagnosed at a young age. This phenomenon presents major governmental, societal, public health and medical challenges to promote healthy lifestyle in the general population to prevent diabetes, screening appropriate individuals including the young for early detection of diabetes and timely optimization of medical care to prevent or reduce the onset of complications. Future research should focus on long-term longitudinal observation of young people with diabetes to ascertain its natural history and effective choice of treatment to prevent or reduce complication-associated morbidity and mortality.

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Conflict of interest: None declared.

References

subjects is characterized by a marked defect in beta cell insulin secretion, severe insulin resistance and a lack of response to aerobic exercise training. Diabetologia 2007; 50:1500–8.
