Current insulin therapy in patients with type 2 diabetes: Results of the ADHOC survey in France

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Abstract

Aim. – In France, the Afssaps/HAS 2006 guidelines for insulin-treated type 2 diabetic patients recommend a target glycated haemoglobin level (HbA1c) of less than 7%, achieved by optimizing the insulin dose or increasing the number of daily injections. The present study investigated to what extent these recommendations are followed in clinical practice by general practitioners (GPs) and diabetologists (DTs).

Methods. – The ADHOC study (observational, transversal) was a survey of 267 GPs and 180 DTs prescribing insulin in France (participation rate: 4.45% and 11.6% of GPs and DTs, respectively). Physicians answered a questionnaire focused on aspects of insulin therapy in type 2 diabetic patients receiving oral antidiabetic drugs (OADs) and insulin for at least six months.

Results. – A total of 1874 patients were included in the study (959 from GPs and 915 from DTs). Insulin was initiated about 10 years after the diagnosis of diabetes, when patients had high HbA1c levels (mean value: 9.2%). At the time of the survey, patients had been treated with insulin for 3.4 ± 3.5 years (mean ± SD), and the mean HbA1c was significantly reduced (P < 0.05) to 7.8% and 7.9% in patients treated by GPs and DTs, respectively. However, almost 80% of patients had HbA1c levels greater than 7%, and 35% had levels greater than 8%. The last fasting blood glucose level was 144 ± 45 mg/dL. More than 60% of patients with HbA1c greater than 8% were using single daily injection therapy. On consultation day, insulin treatment (dose, number of injections and type of insulin) was not optimized in more than 40% of the latter patients. Differences in data between patients treated by GPs and DTs were small and often not statistically significant.

Conclusion. – In this study, the main therapeutic goals of insulin therapy, as defined by the Afssaps/HAS 2006 guidelines, were only attained in around 20% of type 2 diabetic patients, irrespective of follow-up by a GP or DT. During consultation, insulin therapy was not optimized in a large proportion of inadequately controlled patients.

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1. Introduction

It is becoming increasingly apparent that inadequately controlled patients with long-term type 2 diabetes may benefit from the addition of insulin to therapeutic regimens based on oral antidiabetic drugs (OADs) [1–3]. Many factors come into play when deciding at what point to begin insulin therapy and what type of insulin to use [4], but a recent study suggests that adding basal insulin offers the best efficacy-to-safety ratio [5]. In the US, after insulin has been initiated, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend a target glycated haemoglobin level (HbA1c) equal or less than 6.5% [6], whereas the American Diabetes Association (ADA) recommends an HbA1c level less than 7% [7].

In France, the Afsssaps (Agence française de sécurité sanitaire des produits de santé; French Agency for the Safety of Health Products)/HAS (Haute Autorité de santé; National Health Authority) 2006 guidelines recommend combining insulin with OADs when:

- HbA1c is greater than 7% in patients treated with maximum tolerated doses of two OADs (as an alternative to adding a third OAD) and;
- HbA1c is greater than 8% in patients treated with tolerated dosages of three OADs [8].

The aim, in insulin-treated type 2 diabetic patients, is to reduce HbA1c levels to less than 7% [8].

It is recommended to begin insulin therapy with a single daily injection and to optimize the insulin dose with the goal of achieving fasting blood glucose (FBG) levels between 80 and 120 mg/dL. Then, if HbA1c levels are not reduced to less than 8%, the number of daily injections should be increased [8]. The present study investigated whether these recommendations are actually implemented in clinical practice by general practitioners (GPs) and diabetologists (DTs). To this end, a survey (ADHOC) was carried out that focused on antidiabetic therapy and metabolic control of type 2 diabetic patients receiving OADs and insulin for at least six months.

2. Methods

2.1. Study design and participants

This observational, transversal survey was performed among GPs and DTs who were prescribing insulin in France. An invitation to participate in the study was mailed out to 6000 GPs and 1550 DTs who were either private consultants or working in hospitals in France. The GPs were randomly selected from the TVF (Traitement de la Visite médicale et des Fichiers [Medical Treatment and Medical Files], Cegedim, Boulogne-Billancourt, France), ICOMED (Institut de la Communication Médicale [Institute of Medical Communication], Cegedim) and Logimed (Quatrax, Versailles, France) national databases, whereas the DTs were randomly selected from the TVF national database. To avoid selection bias, the physicians were asked to include the first four to six insulin-treated type 2 diabetic patients seen over a period of seven months (from December 2007 to July 2008), with a target total of 2000 patients. A questionnaire was sent to the selected physicians.

2.2. Questionnaire

The questionnaire covered items concerning the general characteristics of both physicians and patients, as well as the patient’s health status and insulin treatments (insulin types, but not pharmaceutical brand names). The HbA1c level was chosen as the primary criterion, while secondary criteria included glycaemia, antidiabetic therapy (insulin, OADs) and diabetic complications (details of the measured parameters are shown in Tables S1–S4; see supplementary material associated with this article online).

2.3. Patients

Participating physicians were asked to include ambulatory type 2 diabetic patients over 18 years of age, and treated with OADs and insulin for at least six months, who agreed to participate in the study. Patients treated with only insulin were excluded. According to the Afsssaps/HAS 2006 guidelines [8], a responder was defined as a patient whose HbA1c level fell...
to less than 7% after at least six months of insulin treatment.

2.4. Statistical analysis

The frequencies and percentages of all categorical responses from the physicians’ questionnaires were calculated. Continuous variables were summarized as means, medians, standard deviation (SD) and range. Statistical significance was analyzed using standard statistical tests. Logistic-regression analysis was used when the target variable was a multifactorial categorical variable with two categories.

To ensure an absolute accuracy of around 2% to describe the proportion of responders, and assuming that 20% of the included patients would not be assessable, the intention was to include 2000 patients.

3. Results

3.1. Participating physicians

Of the 447 physicians who returned a completed questionnaire and were considered as participating in the survey, 267 were GPs and 180 were DTs. Thus, the participation rate was 4.45% and 11.6% for GPs and DTs, respectively.

Table S1 (see supplementary material associated with this article online) shows the characteristics of the 447 participating physicians. They were approximately 50-year-old, mostly men (69%), urban-based (72%) and strictly private consultants (66%), and about one-third belonged to a diabetes network (36%). They were not significantly different from French physicians in the usual databases, such as the Insee (Institut national de la statistique et des études économiques; National Institute of Statistics and Economic Studies), Credes (Consultance en santé publique; Public Health Consulting) and Cnom (Conseil national de l’ordre des médecins; National Council of the College of Physicians), based in Paris, France (www.web.ordre.medecin.fr/demographie/atlas2008).

3.2. Participating patients

A total of 2100 type 2 diabetic patients were included in the study (1056 from GPs and 1044 from DTs). Of these, 226 patients were excluded from the analysis because they failed to meet inclusion criteria. Thus, 1874 patients were retained for the analysis (959 from GPs and 915 from DTs).

Table S2 (see supplementary material associated with this article online) shows the general characteristics of the 1874 analyzed patients. As expected, type 2 diabetic patients were older (age: 64.8 ± 11.2 years), mostly overweight (body mass index [BMI]: 30.1 ± 5.4 kg/m²), and frequently presented with diabetic complications (neuropathy: 25%; fundus abnormalities: 27%), and cardiovascular histories (angina pectoris: 13%; myocardial infarction: 10%; stroke: 6%; lower-limb arteritis: 15%) and risk factors, particularly hypertension (77.5%) and dyslipidaemia (71%). Also, the disorders tended to be slightly milder in patients from GPs compared with those from DTs. The trend was statistically significant for BMI (P = 0.0004), hypertension (P = 0.0091), diet (P = 0.0003) and exercise (P < 0.001).

3.3. Diabetic status of the included patients

Table S3 (see supplementary material associated with this article online) shows the diabetic history of the analyzed patients. Diabetes was diagnosed around 14 years before inclusion in the study (15 years before inclusion by DTs and around 12 years before inclusion by GPs; P < 0.0001). Mean time interval from insulin initiation was 3.35 years (3.75 years vs 2.97 years for DTs and GPs, respectively; P < 0.0001). DTs initiated insulin treatment more frequently in patients treated with two OADs and in those with a slightly, but significantly, higher HbA1c (Table S3; see supplementary material associated with this article online).

Table S4 (see supplementary material associated with this article online) shows the diabetic status of patients and treatment on the day of inclusion in the study. Patients had a mean HbA1c level of 7.83%, which was slightly, but significantly, higher in patients followed by DTs (7.90%) compared with those followed by GPs (7.76%; P = 0.013; Fig. 1).

Fig. 1 compares the HbA1c levels in patients at the time of insulin initiation with values on the inclusion day, and clearly shows that insulin therapy strongly reduced HbA1c to 7.76% and 7.90% in patients treated by GPs and DTs, respectively, although the observed mean values were still higher than those recommended by the Afssaps/HAS 2006 guidelines (< 7%) [8]. Indeed, only around 20% of the studied patients satisfied this requirement (Table S4; see supplementary material associated with this article online). Moreover, 35% of patients had HbA1c greater than 8% (Table S4; see supplementary material associated with this article online) and 14.6% of patients
had both HbA1c greater than 8% and FBG levels greater than 120 mg/dL.

In our studied patients, mean FBG levels were high, with no significant differences between patients treated by GPs (143 ± 41 mg/dL) and those treated by DTs (145 ± 50 mg/dL). The participating physicians all reported hypoglycaemic events in the month prior to inclusion (declarative data). Such events were observed in about one-fifth of patients, with no significant differences between those seen by GPs (17.1%) and those seen by DTs (22.1%).

Microalbuminuria and low creatinine clearance (< 60 mL/min) were less frequently seen in patients treated by DTs (27% and 18% for microalbuminuria and low creatinine clearance, respectively) compared with GPs (41% and 27%, respectively; P < 0.0001). Low-density lipoprotein (LDL) cholesterol was also significantly lower in patients treated by DTs (101 mg/dL) than by GPs (113 mg/dL; P < 0.0001).

3.4. Previous antidiabetic treatment

Most of the consulted patients were treated by mono- or bitherapy with OADs (Table S4; see supplementary material associated with this article online), with no significant differences between GPs and DTs. Most patients also received long-acting insulin analogues (82% vs 78% for GPs and DTs, respectively; P = 0.034). DTs prescribed significantly more premixed insulin (17% of patients) and rapid-acting insulin analogues than did GPs (15.5% of patients; P < 0.0001).

About two-thirds and one-third of patients received single and multiple insulin injections, respectively (Table S4; see supplementary material associated with this article online). Patients from DTs were significantly more often treated with multiple insulin injections than those recruited from GPs (35.8% vs 29.7%, respectively; P = 0.006).

3.5. Diabetic control according to insulin regimen

In patients receiving multiple insulin injections, the target HbA1c of less than 7% was attained in 17.1% and 18.4% of patients followed by DTs and GPs, respectively. In patients receiving single insulin injections, this target HbA1c was attained in 20.9% and 25.3% of patients followed by DTs and GPs, respectively.

Table 1 shows the diabetic status of patients at inclusion according to type of insulin treatment. Of the patients receiving basal insulin alone (long-acting insulin analogue or neutral protamine Hagedorn [NPH]), HbA1c was less than 7% in 22.9%. Of those with an HbA1c greater than 7%, FBG was greater than 120 mg/dL in 78.1% and less than 120 mg/dL in 21.9%. Of the patients treated with a basal–bolus regimen (long-acting insulin analogue or NPH plus at least one rapid-acting insulin), HbA1c was less than 7% in 21.8%. Of those with an HbA1c greater or equal to 7%, FBG was greater or equal to 120 mg/dL in 83.3% and less than 120 mg/dL in 16.7%. Of patients treated by premixed insulin, HbA1c was less than 7% in 13.3% (20% of whom experienced at least one hypoglycaemic episode), and greater or equal to 7% in 86.7%.

3.6. Insulin regimen according to diabetic control

Thirty-five percent of the consulted patients presented with HbA1c greater than 8% (Table S4; see supplementary material associated with this article online), but less than 40% of them received multiple daily injections (Fig. S1, upper; see supplementary material associated with this article online). Thus, 407 patients (21.7% of the total) had HbA1c greater than 8% and received single daily injections.

3.7. Antidiabetic treatment decisions

Insulin therapy: Fig. S1 (lower; see supplementary material associated with this article online) shows the medical decisions made for the 21.7% of patients with HbA1c greater than 8% and receiving single daily injections. In 60% of these cases, the insulin dose was increased, but few were switched to multiple daily doses. The GPs sent 60% of these patients to a DT. In 119 patients (6.35% of the total), insulin therapy remained unchanged, and their GPs did not send them to a DT. The only remarkable feature in these patients was high FBG (mean: 157 mg/dL), with 82.6% exhibiting FBG levels greater than 1.2 g/L.

OADs: OAD treatment was intensified in a small proportion of patients: OAD doses were increased in around 10% of patients; and a new OAD was added to around 10% of patients with HbA1c levels greater than 8%, and to 5% of patients with HbA1c levels of 7–8%.

3.8. Characteristics of patients with high HbA1c levels at inclusion

Patients were divided into two groups according to HbA1c levels at inclusion: HbA1c greater or equal to 7.7% (n = 938), and HbA1c less than 7.7% (n = 921) (median HbA1c value: 7.7%). Logistic-regression analysis showed that the group of patients with HbA1c greater or equal to 7.7% had significantly lower prevalences of cardiovascular complications (relative risk [RR]: 0.71; 95% confidence interval [CI95%]: 0.55, 0.93; P = 0.0123), higher last capillary blood glucose values (RR: 24.38; CI 95%: 15.34, 38.76; P < 0.0001) and higher HbA1c values at insulin initiation (RR: 1.61; CI95%: 1.45, 1.80; P < 0.0001).

4. Discussion

Numerous guidelines offer insulin treatment recommendations for type 2 diabetic patients [6–8], but few studies have been dedicated to investigating how they are implemented in clinical practice. To our knowledge, ADHOC is the first study to evaluate everyday routine practices in terms of insulin therapy in type 2 diabetic patients since the introduction of long-acting insulin in France (the type of insulin given to 80% of the 1874 patients analyzed here).
One important observation of the ADHOC survey is that, after more than six months of insulin treatment (3.4 years in average), almost 80% of type 2 diabetic patients still had HbA1c levels greater than 7%, irrespective of being followed-up by a GP or a DT. This indicates that:

- the main therapeutic goal of insulin therapy, as defined by the Afssaps/HAS 2006 guidelines [8] was attained in only around 20% of patients;
- and patients arrived at the consultation with high FBG levels (mean: 144 mg/dL).

In addition, multiple insulin injections were found in less than 40% of patients with HbA1c greater than 8%. Furthermore:

- insulin was initiated about 10 years after the diagnosis of diabetes, when patients had HbA1c levels of 9.2% (mean value);
- and insulin treatment (dose, number of injections, type of insulin) was not optimized in a high proportion of patients (therapeutic inertia).

Whether there are genuine difficulties in attaining guideline objectives and in optimizing insulin therapy in everyday clinical practice require further discussion and investigation.

One methodological problem to be considered is whether a survey is an accurate reflection of how guideline recommendations are followed. Indeed, our study was declarative and transversal, whereas a longitudinal study would have allowed better evaluation of treatment efficacy. Furthermore, the selection by physicians of their first four to six patients could have led to the inclusion of sicker patients or those with greater compliance to treatment, as such patients are more likely to visit their healthcare provider more often. The physicians who participated are also much more likely to be involved in diabetes care. Also, our observational study may have induced interventions, leading to a potentially higher rate of treatment change than usual.

Finally, a 7% HbA1c target is relevant only for patients with strict targets, which was probably the case for the majority, but not necessarily all, of the patients, given their average age and cardiovascular complication rate. Thus, the present results require confirmation by well-designed clinical trials. Nevertheless, our findings are clear-cut, obtained from a large proportion of patients attending representative GPs and DTs, and included evaluated medical decisions during consultations. Moreover, these results confirm and extend previous observations.

Insulin is being increasingly used for the treatment of type 2 diabetes, as shown by the ECODIA studies conducted in 1999 and 2005 [9]; insulin was used by 5% of the selected patients in 1999 and 14.1% in 2005. Similarly, insulin use in drug-treated type 2 diabetic patients increased from 17% in 2001 to 19% in 2007, according to the ENTRED studies [10]. However, despite this growing insulin use, the time between insulin initiation and diagnosis of the disease, and the HbA1c level at the time of insulin initiation, do not appear to have changed over time. The mean time to insulin initiation found in the present study (10 years) is in line with those found in the ECODIA 2 study (10.2 years) [9] and IDAHO 1 study (12 years) [11] conducted in 2005 and 2002, respectively. Also, our high HbA1c level at insulin initiation (9.2%) is similar to that described in the IDAHO 1 study (9.5%) [11].

These data confirm the therapeutic inertia already demonstrated in ECODIA 2, where 23% of patients treated with several OADs still had HbA1c levels greater than 8%, and in the ENTRED 2001/2003 study, where only one-fourth of the type 2 diabetic patients receiving at least two OADs and with an HbA1c greater than 8% started insulin within the subsequent two years [12]. This suggests that the Afssaps/HAS recommendation to initiate insulin when HbA1c reaches 8% [8] is still far from being followed in clinical practice. Our finding that the HbA1c at the time of insulin initiation is a strong marker of the HbA1c value 3.4 years later militates in favour of earlier insulin treatment.

The high level of HbA1c (7.8%) found in our present type 2 diabetic patients treated with insulin for at least six months is also similar to that reported in the ECODIA 2 study (8%) [9]. Thus, the Afssaps/HAS therapeutic goal for insulin-treated patients (HbA1c < 7%) [8] was attained in only around 20% of the patients in our survey. Furthermore, 35% of patients still had an HbA1c greater than 8% despite insulin, although this was an improved proportion compared with that found in ECODIA 2 (43%).

According to their HbA1c and FBG levels, and the Afssaps/HAS 2006 guidelines for insulin-treated patients [8] (HbA1c target value < 7% and, in patients receiving basal insulin, FBG target level < 120 mg/dL), of the patients treated with long-acting insulin analogues or NPH alone, 60% demonstrated insufficient insulin titration, and 17% should have received a more complex insulin regimen with the addition of one or several rapid-acting

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### Table 1

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>LAIA or IAI alone</th>
<th>LAIA or IAI + RAI</th>
<th>Premixed insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1190</td>
<td>188</td>
<td>150</td>
</tr>
<tr>
<td>HbA1c &lt; 7% (% patients)</td>
<td>22.9</td>
<td>21.8</td>
<td>13.3</td>
</tr>
<tr>
<td>HbA1c ≥ 7% and:</td>
<td>77.1</td>
<td>78.2</td>
<td>86.7</td>
</tr>
<tr>
<td>FBG &lt; 120 mg/dL (% patients)</td>
<td>21.9</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>FBG ≥ 120 mg/dL (% patients)</td>
<td>78.1</td>
<td>83.3</td>
<td></td>
</tr>
</tbody>
</table>

LAIA: long-acting insulin analogue; IAI: intermediate-acting insulin; RAI: rapid-acting insulin; FBG: fasting blood glucose.
insulin analogues (Table 1). Of the patients already receiving a basal–bolus regimen, 65% had insufficient basal insulin titration and 13% had insufficient rapid-acting insulin titration. Of those treated with premixed insulin, 87% needed more complex insulin treatment, such as a basal–bolus regimen. Overall, given that all patients have an HbA1c target of less than 7%, 78% needed more intensified insulin treatment (with either more titrated doses or more injections).

On considering only the less well-controlled patients (HbA1c > 8%), insulin therapy was unchanged in 18.1%, in spite of FBG levels as high as 157 mg/dL.

The diabetic condition of patients followed by DTs tended to be similar than those of patients followed by GPs, with differences that were often small and/or not statistically significant. On the other hand, participation in a diabetes network can facilitate the adoption of guidelines by local physicians. These considerations suggest a need for better coordination between DTs and GPs, an aspect that is beyond the scope of this report.

In France, the prevalence of treated diabetes has progressed inexorably from 2.7% of the population in 2000 to up to 3.6% and 3.95% in 2005 and 2007, respectively [13, 14]. This suggests that an effort needs to be made to define the future direction of insulin therapy. In this respect, the observation that the doses or number of daily injections were not maximized in a high proportion of patients clearly shows that there is still room for improvement of insulin therapy with the currently available tools.

5. Conclusion

The present survey found that insulin therapy in type 2 diabetic patients was initiated after a delay of around 10 years after diagnosis, when patients had high HbA1c levels (9.2%). After a mean duration of 3.35 years of insulin treatment, almost 80% of patients still had HbA1c levels greater than 7%, and more than 60% of those with HbA1c greater than 8% were receiving single daily injection therapy. On consultation days, insulin treatment (dose, number of injections) was not optimized in more than 40% of the latter patients, despite their high FBG levels. Differences between patients seen by GPs and by DTs were small, and often not statistically significant. In summary:

- the main therapeutic goals of insulin therapy, as defined by the Afssaps/HAS 2006 guidelines [8], were only attained in around 20% of type 2 diabetic patients;
- and insulin therapy was not optimized in a large proportion of inadequately controlled patients.

Thus, it is therapeutic inertia that delays insulin initiation and insulin therapy optimization.

Disclosure of interest

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Appendix A. Supplementary data

Supplementary material associated with this article can be found at http://www.sciencedirect.com, at doi:10.1016/j.diabet.2011.03.001.

References