http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **23**(1):087-094
doi: 10.1515/rjdnmd-2016-0011

INSULIN INITIATION IN TYPE 2 DIABETES – WHY, WHEN AND HOW?

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received: January 31, 2016 *accepted*: February 16, 2016
available online: March 15, 2016

Abstract

Type 2 diabetes is a progressive disease and, despite recent progress in the treatment of diabetes, the glycemic control usually deteriorates gradually and insulin therapy is needed. When insulin therapy should be started and which are the appropriate insulin therapy strategies, still represent subjects of debates. Insulin represents a therapeutic option in type 2 diabetes due to the existence of early β-cell dysfunction and significant reduction of β-cell mass in natural history of type 2 diabetes. The current guidelines recommend insulin in double therapy in association with metformin or in combination with metformin and other noninsulin agent. Initiation of insulin therapy is recommended in patients with newly diagnosed type 2 diabetes and symptomatic and/or presenting important hyperglycemia or elevated HbA1c. Initiation of insulin therapy in type 2 diabetes should take into consideration the pathophysiology of type 2 diabetes, the effects and the potential risks of insulin therapy, the guidelines recommendations and the barriers to insulin use. Literatures of only English language were analyzed from NCBI database. Guidelines were accessed electronically from organisations, i.e. American Diabetes Associations, American Association of Clinical Endocrinologists and American College of Endocrinology, European Association for the Study of Diabetes, International Diabetes Federation.

key words: *Type 2 diabetes; insulin therapy; β-cell dysfunction; diabetes guidelines*

Introduction

Type 2 diabetes mellitus (T2DM) is a major public health concern with an exponentially increasing prevalence, leading to clinical, therapeutic, social and economical consequences at the global level. Screening, early diagnosis and proactive management of T2DM can help control progression of diabetes and its complications.

T2DM is a progressive disease and, despite recent progress in the treatment of diabetes, the glycemic control usually deteriorates gradually and insulin therapy is needed in many cases [1,2].

When insulin therapy should be started and which are the appropriate insulin therapy strategies, still represent subjects of debate.

Insulin therapy in T2DM should aim to achieve and maintain optimal glycemic control in order to reduce the risk of micro- and

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macrovascular complications, to improve patient quality of life and to reduce the healthcare diabetes–related cost.

Initiation of treatment with insulin in T2DM should take into consideration several factors including the underlying pathophysiology of T2DM, the glycemic, non-glycemic effects and also the potential risks of insulin therapy, the recommendations of guidelines from professional societies, coexisting physiologic and medical conditions and the possible barriers to insulin use.

Despite recent progresses and discoveries in the area of insulin therapy, insulin remains underutilized and over 60% of patients are not reaching glycemic targets [3].

The present review highlights the factors which transfer the insulin initiation from guidelines to real-life practice.

Methods

Literature of only English language was analyzed from electronic databases search. Sources of the original studies and review papers were collected from NCBI database, using following search index terms: "insulin initiation type 2 diabetes", "β-cell dysfunction in type 2 diabetes", "insulin therapy". We have also gathered information from guidelines and articles accessed electronically from organisations, i.e. American Diabetes Associations (ADA), American Association of Clinical Endocrinologists and American College of Endocrinology (AACE), European Association for the Study of Diabetes (EASD), International Diabetes Federation (IDF) and Canadian Diabetes Association (CDA).

Place of β-cell dysfunction in natural history of type 2 diabetes

T2DM is a progressive condition caused by genetic and environmental factors that induce tissue insulin resistance and β-cell dysfunction [4]. Based on the United Kingdom Prospective Diabetes Study (UKPDS) study estimates that at diagnosis of T2DM, β-cell function is already reduced by 50% and that this reduction of β-cell function seems to start with 10-12 years before the appearance of hyperglycemia [5,6].

In the early stage of T2DM, β-cell dysfunction predominates even if there is a significant reduction of β-cell mass [7]. The typical functional alterations in diabetes are represented by elevation of threshold for insulin secretion triggering, disappearance of first-phase and prolongation of second-phase insulin secretion after stimulation by intravenous glucose and maintenance of basal insulin secretion [8,9].

Consequent deterioration in metabolic equilibrium with increasing levels of glucose and free fatty acids, enhance and accelerate β-cell dysfunction, lead to beta cell apoptosis and subsequent decrease of β-cell mass [10,11].

Butler et al. indicated that obese subjects with impaired fasting glycemia (IFG) or T2DM had 40-63% reduction of β-cell volume comparing with non-diabetic obese subjects and that non-obese subjects with T2DM had 41% reduction of β-cell volume comparing with non-obese non-diabetic subjects [7,12]. Marchetti et al. showed that T2DM subjects had a reduced number of β-cell and a 40-50% reduction of density volume of mature insulin granules [13]. In T2DM, decreased β-cell mass is mainly due to enhanced β-cell apoptosis that does not seem to be adequately compensated by regenerative process in diabetic islet [7].

Taking into consideration the existence of early β-cell dysfunction and significant reduction of β-cell mass in natural history of T2DM and the progressive character of these pathophysiological modifications, insulin therapy could be an important option for obtaining and maintaining optimal glycemic

control. Increasing insulin levels by exogenous insulin administration for the control of hyperglycemia may appear initially contraindicated in patients with evidence of insulin resistance, so it is imperative to simultaneously address insulin resistance with metformin [14].

Benefits and risks of insulin therapy

The main objectives of insulin therapy in patients with T2DM are represented by the prevention of diabetic chronic and acute complications and maintaining quality of life [15]. Several large scale studies on patients with T2DM indicated that intensive insulin therapy lead to improvement of glycemic control and decrease the risk of chronic micro- and macrovascular complication [16,17]. In T2DM patients treatment with insulin reduces lipolysis, regulate cholesterol ester metabolism in macrophages, therefore having beneficial effects on atherogenic dyslipidemia [18].

Hypoglycemia is the most common and most serious side effect of insulin. Post hoc epidemiological analysis of the ACCORD study indicated that the risk of severe hypoglycemia was significantly higher in patients with neuropathy, with long diabetes duration and with serum creatinine >88.4 μmol/l [19]. Comparing long-acting insulin analogues with NPH in T2DM, Horvath et al. demonstrated that both insulin glargine and detemir have led to a significant risk reduction of symptomatic and nocturnal hypoglycemia compared with NPH [20].

Weight gain represents a considerable challenge in T2DM patients with insulin therapy and a frequent cause of delay in initiation of treatment with insulin [21]. Several long-term studies indicated that in patients with intensive insulin therapy there was a higher rate of weight gain compared with patients with conventional insulin therapy [16]. On the other hand Shan et al. showed that intensification of insulin therapy causes modest weight and no changes in body fat distribution or liver fat in obese patients with T2DM [22]. In patients with insulin therapy, decreasing daily caloric intake, optimization of lifestyle and increasing the frequency of glucose self-monitoring in order to detect hypoglycemia represent potential options for prevention of body weight gain [23].

Cancer risk represents a major concern in T2DM patients with insulin therapy. Several epidemiological studies and meta-analyses indicate increased cancer risk in patients with T2DM which could be attributed to long-term exposure to elevated insulin concentrations come from insulin resistance or exogenous insulin administration [24]. In accordance with epidemiological studies, experimental models have demonstrated a positive correlation between insulin concentration and cancer risk, particular concerns being raised by insulin analogues [25,26]. However these data are controversial and difficult to interpret.

Regarding the rates of *all-cause and cardiovascular mortality* related with insulin therapy, Gamble et al observed a significant and graded association between all-cause and cardiovascular mortality risk and insulin exposure level in an inception cohort of patients with type 2 diabetes [27].

Insulin therapy in type 2 diabetes management

The conservative management of T2DM included lifestyle modification followed by treatment with oral antidiabetic (OAD) monotherapy, which is often titrated upwards to maximal recommended doses before combination therapy is introduced [28]. This traditional "stepwise" approach to T2DM management often leads to long periods of hyperglycemia before the treatment is stepped up

which may increase the risk of micro- and macrovascular complications [29].

A more proactive approach is necessary in order to optimise patient care. This represents the same sequence of events of treatment but with each stage brought forward. Insulin therapy could be an appropriate option to provide better and more rapid glycemic control in patients with T2DM [30].

Still remains question regarding the appropriate moment for insulin therapy initiation in type 2 diabetes patients. In T2DM, insulin therapy is clearly indicated in case of failure therapy with maximally tolerated doses of OAD, OAD contraindications (hepatic or renal impairment), reduced tolerance/allergy to OAD, episodes of acute metabolic stress (infection, acute abdomen, myocardial infarction, stroke, etc), acute complications of diabetes (diabetic ketoacidosis, hyperglycaemic hyperosmolar state), pregnancy and lactation, pre -, intra - and postoperative [31].

If in these particular situations the necessity of insulin therapy is easy to understand, it is difficult to identify the optimal timing of insulin therapy initiation and predict the patients with T2DM who will require insulin therapy.

Recent studies indicated that early insulin therapy induces recovery of β-cell function and diabetes remission in subjects with newly diagnosed T2DM [32]. Alvarsson et al. indicated that insulin therapy is superior in preservation of β-cell function, compared with sulphonylurea, in recently diagnosed type 2 diabetic patients [33].

Short-term insulin therapy may lead to a better response at a subsequent intervention with oral antidiabetic drugs (OAD) associated with lifestyle optimization measures in previously untreated patients with high level of glycemia at the moment of T2DM diagnosis [34]. Usually these patients have had diabetes for a relative short time and are likely to achieve normal glycemic control under insulin therapy and the transition from insulin to oral hypoglycaemic agents may be feasible [34]. Some patients recently diagnosed with T2DM may have had diabetes for several years and therefore long-term insulin therapy alone or in combination with OAD might be the only option [35].

Prediction of patients with T2DM who will need insulin therapy is important in order to avoid unacceptable delays in both achieving and maintaining glycemic goals.

Recent studies indicated that fasting and postprandial C-Peptide indices (serum C-peptide level adjusted by plasma glucose level) reflect β-cell insulin secretion capacity and those could predict the necessity of insulin therapy [35,36].

Insulin therapy in guidelines

The American Diabetes Association and the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend basal insulin in association with metformin in double therapy and in association with metformin and other additional noninsulin agent [37,38].

Consensus guidelines from the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) recommends insulin therapy as a first line in patients with initial HbA1c>10% and as the second line after failure of metformin monotherapy in patients who are symptomatic or have HbA1c>8,5%. In treated patients whose HbA1c remains >7%, insulin therapy should be initiated or dose titrated upward [14].

The International Diabetes Federation (IDF), the Canadian Diabetes Association (CDA) use an algorithm in which insulin therapy is mostly reserved when optimized oral glucose-lowering drugs and lifestyle interventions are unable to maintain glycemic control at target levels [39,40].

All these consensus statements make exception for the patients with very high levels of glycemia (≥300-350 mg/dl) or HbA1c (≥9%), with symptomatic diabetes or acute metabolic disequilibrium and patients with contraindication to noninsulin antidiabetic drugs [37,38]. These patients should start insulin therapy immediately along with lifestyle optimisation [37,38].

Insulin therapy strategies in type 2 diabetes

In T2DM, the gradual decline in insulin secretion over time requires the addition and intensification of insulin to ongoing OAD in order to obtain and maintain optimal glycemic control [4].

An insulin therapy strategy is ideal when exogenous insulin replacement mimics the physiologic basal and prandial insulin secretion [41].

In T2DM there are three distinct insulin strategies: basal insulin plus OAD, combination of basal and prandial insulin and premixed insulin.

Adding basal insulin to OAD is indicated to patients with HbA1c between 7.0 and 10.0% despite 2 oral medications [42,43]. Adding long-acting insulin to OAD therapy in T2DM patients leads to significant decrease of HbA1c. If HbA1c remains >7% and postprandial glycemia level is elevated it is recommended to add prandial insulin starting with largest daily meal. Patients with HbA1c >10% despite oral therapy are likely to require prandial insulin addition to basal insulin. An alternative strategy is the use of premixed insulin but they do not provide physiologic insulin coverage [43]. In case of using basal-prandial or premixed insulin regimes, metformin should be continued but the oral secretagogues should be discontinued [43].

Several studies (INITIATE, DURABLE) have shown the superiority of long acting insulin basal analogue glargine compared with premixed insulin in reducing HbA1c in terms of lower insulin dose and fewer adverse events such as symptomatic hypoglycaemia and weight gain [44,45].

Implementation of insulin therapy

Several studies indicated that, despite the potential benefits of early insulin therapy in patients with T2DM, delays in starting insulin are common, even when glycemic control is inadequate [46]. Clinical inertia in response to inadequate glycemic control by adding insulin proved to be significantly lower in primary care compared with specialist care [47]. Negative patient concerns regarding initiation and intensification of insulin therapy include fear of injection, lifestyle limitation caused by the treatment, necessity of glycemic self-monitoring, adverse events of insulin therapy such as hypoglycaemia [48,49]. Frequently patients may perceive insulin as a sign of their personal failure to control diabetes and only a small number of patients believe that insulin will help to improve glucose control [48,49].

Health care practitioners concerns include hypoglycaemia, weight gain, cardiovascular risk and insulin-related cancer risk [41]. In addition, both clinicians and patients may consider insulin therapy to be complicated and labour-intensive.

Many patient-related barriers could be removed by the explanation from the time of diagnosis the fact that T2DM tends to progress and that insulin is one of the options available to aid management of their diabetes [49]. Once insulin is initiated, the education (including on continuing lifestyle management and appropriate self-monitoring) should be provided and the patients should be empowered to take active control of their own diabetes management [37,38].

Conflict of Interest: all authors declare that they have no conflict of interest.

Funding: Not applicable.

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