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Do All Evidences Say that the Insulin Analogues are More Effective Than Human Insulins?

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ABSTRACT

Optimal blood glucose levels are maintained by the treatment of insulin. Recently Insulin Analogues and Insulin treatment Regimens are developed to meet the needs for the maintenance optimal blood glucose levels. The United States, as a country that has already faced with a significant increase in diabetes-related costs, made a remark in ADA standards of care 2020 on the importance of insulin costs underlying that choice of basal insulin should be based on patient-specific considerations, including cost. Comparative Effectiveness and Safety of Premixed Insulin Analogues in T2D" 16 studies that compared premixed IA with premixed RHI were analyzed. The pooled analysis suggested that premixed IA provide similar hba1c control to premixed RHI and similar fasting plasma glucose level control to premixed RHI. Premixed IA were more effective than premixed RHI in decreasing postprandial plasma glucose levels. Premixed IA may cause similar rate of incidents of hypoglycemia as premixed RHI. The increase in costs due to the increase in the cost of insulin therapy has long resembled a snowball. Such a development of situation insistently tells us that effective program policies are needed to optimize costs on the one hand, and increase the ubiquitous availability of insulin, on the other hand. These two interrelated processes along with the prevention of the development of diabetes mellitus and its complications, including due to the popularization of non-drug approaches (healthy eating, physical activity as a way of life, smoking cessation and minimization of the influence of other modifiable risk factors) should become cornerstones of helping people with diabetes.

Keywords: Insulin analogues, Recombinant human insulin, American diabetes association, Hypoglycaemia

INTRODUCTION

Insulin treatment is a necessity for the lives of patients with diabetes to maintain optimal blood glucose levels. In recent years, new insulin analogues (IA) and various insulin treatment regimens have been developed to meet these needs. On the other hand, new insulin formulations create higher costs, which may limit their use. Factors such as the effectiveness of treatment, its safety and patient satisfaction should be taken into account when decision on choosing the right treatment made, but their cost also cannot be ignored, taking in consideration that these drugs are subject to reimbursement. In order to fulfill these prerequisites and to account for the chronic course of the disease, insulin therapy should be tailored individually to the patients' needs, treatment goals, safety and costs.

Global insulin market is growing and predicted to reach USD 76 bln till 2023 [1]. In view, that most of diabetes cases diagnosed in the countries with low and middle income, price should be seriously considered as one of the most important characteristics and marketing of the most expensive products should be responsible as never been before.

Currently, there is a wealth of data comparing recombinant human insulin's (RHI) to insulin analogous (IA), including meta-analyzes of comparative efficacy and safety, as well as cost-effectiveness data as well as data related to possible malignancy.

Authors propose an analysis of these data regarding the appropriateness of using IA vs RHI in type 1 (T1D) and type 2 (T2D) diabetes mellitus and their effectiveness in both types of diabetes.

According to Management of T2D NICE guidelines (2008) the recommendations are to usually start insulin treatment with human neutral protamine Hagedorn (NPH) insulin.

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However, a long-acting basal insulin may be considered in some circumstances such as special risk from hypoglycaemia, and where twice daily injection is problematic [2].

In regards to ADA/EASD Consensus (2009) [3], the very rapid-acting and long-acting insulin analogues have not been shown to lower A1C levels more effectively than the older, rapid-acting or intermediate-acting formulations [4-6].

According to ADA (American Diabetes Association) standards of medical care in diabetes - 2018 most individuals with T1D should use rapid-acting insulin analogs to reduce hypoglycemia risk. In T2D it is recommended to initiate insulin therapy with basal NPH insulin, in case of lack of effectiveness to add one rapid acting insulin before main meal or to switch to premixed insulins, in case of further lack of effectiveness to switch to pre-mixed insulin analogs or to add additional injection of rapid acting insulin [7]. This year ADA standards of medical care in diabetes-2020 [8] already says that to initiate insulin in patients with T2D doctors should consider basal insulins with low hypoglycemic effect. Same recommendation edited European Society of cardiologists (ESC) together with European Association of Study Diabetes (EASD) [9]. Russian algorithms of medical care 2019 goes father and place an open recommendation to start insulin therapy in type 2 patients with IA.

The United States, as a country that has already faced with a significant increase in diabetes-related costs, made a remark in ADA standards of care 2020 on the importance of insulin costs underlying that choice of basal insulin should be based on patient-specific considerations, including cost.

NICE T2D guidelines revised in 2019 [10], do not contain direct recommendation to start insulin therapy at T2D patients from IA, but recommends to start from a choice of a number of insulin types and regimens: offer NPH insulin injected once or twice daily according to the need. Consider starting both NPH and short-acting insulin (particularly if the person's HbA1c is 75 mmol/mol (9.0%) or higher), administered either: separately or as a pre-mixed (biphasic) human insulin preparation. Consider, as an alternative to NPH insulin, IA if: the person needs assistance from a career or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine [11] would reduce the frequency of injections from twice to once daily or the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if a person prefers injecting insulin immediately before a meal or hypoglycemia is a problem or blood glucose levels rise markedly after meals [10]. We'll write below about hy possible reasons wGB hesitates to follow common trend. There are also rather confusing data regarding usage of long acting insulin analogues in T1D and T2D – they aren't recommended for T1D but recommended as a first choice for T2D in latest ADA and ESC/EASD standards.

Another discussion could be taken in regard to usage premixed insulin analogous.

Premixed insulin formulations are among the most frequently used in many countries [12]. There are apparent differences in pharmacokinetic and pharmacodynamics properties between premixed insulin IA and conventional premixed RHI [13]. Whether the differences possess a clinical importance remains a matter of discussion and surely depends on an individual patient clinical condition [11]. However, IA may not be suitable for all patients with diabetes. For many patients, a disadvantage regarding the application of IA may be a therapy expense [10,11] as well as too short time of action among individuals by whom insulin formulation requires a longer time span, for example, those who used to eat snacks.

It is very important to implement insulin therapy to patients who are likely to adhere, because nonadherence to pharmacotherapy has been linked to unfavorable outcomes [14].

Use of RHI and IA among patients with T2D

In Systematic Review "Comparative Effectiveness and Safety of Premixed Insulin Analogues in T2D" 16 studies that compared premixed IA with premixed RHI were analyzed. The pooled analysis suggested that premixed IA provide similar HbA1c control to premixed RHI and similar fasting plasma glucose level control to premixed RHI. Premixed IA were more effective than premixed RHI in decreasing postprandial plasma glucose levels. Premixed IA may cause similar rate of incidents of hypoglycemia as premixed RHI. Study's conclusion is that premixed IA provide glycemic control similar to that of premixed RHI and may provide better glycemic control than long-acting IA and noninsulin antidiabetic agents, but data on clinical outcomes are very limited [15].

The observational study PROGENS Benefit aimed to compare efficacy, safety, and quality of treatment satisfaction of premixed RHI and IA among T2D patients, showed that premixed insulin both IA and RHI are efficient and safe, and studied patients were satisfied with both treatment methods [16].

According to another study comparing of efficacy and safety of premixed RHI insulin (Gensulin M30) with premixed insulin Aspart 30/70 (NovoMix30) in patients with T2D mellitus [17]. FPG, PPG and HbA1c values did not differ significantly between subgroups of patients. Incidence of severe and mild hypoglycemia did not differ significantly between subgroups of patients. Treatment with pre-mixed

insulin Gensulin M30 or NovoMix30 for at least half a year results in similar metabolic control of patients (FPG, PPG and HbA1c). Safety of treatment with pre-mixed RHI (Gensulin M30) or IA (NovoMix30) is similar.

According to review of the evidence comparing insulin (human or animal) with IA [12] in analyses that indicated statistically significant advantages for IA for glycaemic control, the differences between IA and RHI remain very small (ie 0.09%) and do not constitute clinically important differences. Consequently, the available evidence indicates that IA have no advantage over RHI for the outcome of glycaemic control.

Regarding the occurrence of hypoglycaemic events, IA appear to have statistically significant advantages compared to RHI, but these advantages are not consistent across types of insulin (rapid or long-acting) or types of diabetes, and the clinical importance of these differences is not clear. In addition, many trials which demonstrated a difference between analogue insulin and regular human insulin for the occurrence of hypoglycaemia excluded patients with a history of recurrent major hypoglycaemia [18]. Therefore, it may not be appropriate to assume such advantages will be observed across all patients.

Another systematic review and meta-analysis included eight studies comparing the effects of long-acting IA to RHI in patients with T2D. Six studies investigated insulin glargine and two insulin detemir. No superiority in HbA1c was observed for insulin glargine. For insulin detemir the meta-analysis yielded a statistically significant but clinically unimportant superiority of RHI in metabolic control. Symptomatic and nocturnal hypoglycaemic events were lower in patients treated with insulin glargine than in patients with RHI therapy. Also, for insulin detemir the two included studies found a lower number of patients experiencing overall or nocturnal hypoglycaemic episodes in the insulin detemir treatment groups. The methodological quality of the included studies allowed only a cautious interpretation of the results.

Up till now, no study designed to investigate possible long-term effects was found. Therefore, it remains unclear if and to what extent the treatment with long-acting IA will affect the development and progression of microvascular and macrovascular events compared to results obtained with RHI. Since the differences in overall effects on metabolic control were only small for insulin glargine and RHI and even disadvantageous for insulin detemir, no important improvements in the development of microvascular late complications would be expected from treatment with long-acting IA.

As for the advantages found in the rate of severe hypoglycaemic events some caution is warranted. No statistically significant advantage was found for therapy with insulin glargine or detemir. Also, interpretation of the results of the frequency of severe hypoglycaemiais difficult due to bias-prone definitions. Patients may inappropriately deny severe hypoglycaemia and in this context “third party help” is a soft and variable description of severity. More robust definitions as “injection of glucose or glucagon by another person” may result in more reliable data [19]. In all studies the frequency of severe hypoglycaemia was very low, making it unlikely to see an important clinical effect for the different treatments. Even though the meta-analysis found a consistent reduction in symptomatic or overall hypoglycaemic effects for therapy with long-acting IA, no safe inferences can be drawn from these results because defining hypoglycaemia by symptoms only makes the results prone to bias, especially in open trials with (likely) no blinded outcome assessment. The advantage of insulin glargine and detemir could be a lowering of nocturnal hypoglycaemic events in patients with T2D mellitus and treatment with basal insulin. But again, bias cannot be ruled out and thus makes the interpretation of the results difficult.
No trial reported data on quality of life. One trial reported data on treatment satisfaction [20] and reported a more pronounced improvement in therapy satisfaction in patients treated with insulin glargine. The interpretation of the clinical importance of this result is hindered by the fact that baseline and end of trial values are reported even though the trialists claim a statistically significant improvement in the change of treatment satisfaction. Additionally, the reporting of this outcome was poor and therefore the assessment of the quality of this outcome was not possible.

Short-acting IA versus RHI in patients with DM were investigated in Cochrane 2008 Review. The main objective of this systematic review was to assess the effects of short-acting IA in comparison to RHI in patients with T1D and T2D. Were found no statistically significant differences in long-term metabolic control (HbA1c) between short-acting IA compared to RHI in patients with T2D; no statistically significant differences in overall hypoglycemic episodes between short-acting IA compared to RHI in T2DM patients: 3 studies [one double blind, two open design] found no significant difference between RHI and IA; 4 studies observed improvement in patients’ treatment satisfaction in the IA group (mainly due to the changes in convenience, flexibility and continuation of treatment as well as injection-meal interval). As a conclusion the systematic review suggests only a minor clinical benefit of short-acting IA in the majority of patients treated with insulin [4].

Another study compared fast-acting insulin analogues vs RHI (long-acting insulin analogues vs NPH and ready-made mixtures of insulin analogues vs ready-made mixtures of human insulin) in patients with type 1 and type 2 diabetes and women with gestational diabetes. The aim of the study was to determine the benefits in terms of glycemic control and possibility to reduce the risk of complications and side effects. A systematic review of randomized clinical trials was conducted. The results showed that the differences in HbA1c

levels and the incidence of hypoglycemia were insignificant and cannot be considered as clinically significant. In accordance with the opinion of the authors of the study, insulin analogues do not have advantages in terms of glycemic control, but can be useful in the treatment of patients with repeated hypoglycemia while optimizing the existing treatment with human insulin. The routine use of long-acting insulin analogues in type 2 diabetes mellitus is not recommended due to the high cost/effectiveness ratio [21]. Rapid acting insulin analogs have significantly different pharmacokinetics and pharmacodynamics compared to human insulin. Based on these results, it is widely believed that regular insulin should be administered 20-30 min before a meal in order to lower the concentration of glucose in postprandial blood compared to an insulin analogue administered immediately before a meal. The interval between injection and food intake for patients with type 2 diabetes is not necessary [22]. A systematic review of 28 studies (10 with type 2 diabetes) showed that short-acting human insulin and the rapid acting analog of isulin (aspart) helped to achieve identical glycemic control in type 2 diabetes, and that the same results were achieved when evaluating HbA1c and the incidence of hypoglycemia, including risk severe hypoglycemia. In this case, short-acting human insulin showed the best results for the control of fasting glycemia, and the rapid acting analog of isulin (aspart) showed the best results for the control of postprandial glycemia [23]. Another study conducted in Germany showed that the long-term benefits of using long-acting insulin analogues for type 1 diabetes mellitus as a whole have not been adequately studied, and there is no evidence of the benefits of insulin glargine and insulin detemir compared with NPH insulin [24].

The study of the use of long-acting insulin analogues in type 2 diabetes [25] showed that patients who are not on intensive insulin therapy have no evidence of the benefits of insulin glargine and insulin detemir compared with NPH insulin; during intensive insulin therapy, the basal insulin regimen in combination with oral hypoglycemic drugs also lacks evidence of the benefits of insulin glargine and detemir insulin compared to insulin NPH, provided that human insulin therapy has been optimized. It was noted that, in general, the long-term benefit of using long-acting insulin analogues in terms of the impact on the development of late complications of diabetes is not well understood. A study of the use of fast-acting insulin analogues in type 1 diabetes mellitus [26]. showed that the benefits of aspart as compared to human insulin in adult patients are not obvious because of lack of data; in patients with a higher than average risk of hypoglycemia, the same result was demonstrated with the use of lyspro insulin and human insulin, and the benefits of lyspro insulin in patients with a high risk of severe hypoglycemia are not obvious; due to the lack of data, we can't talk about the advantage of insulin glulisin compared with human insulin.

Another analysis suggests, if at all only a minor clinical benefit of treatment with long-acting IA for patients with T2D treated with "basal" insulin regarding symptomatic nocturnal hypoglycaemic events. Until long-term efficacy and safety data are available, we suggest a cautious approach to therapy with insulin glargine or detemir.[4].

Cost-effectiveness Approaches to Insulin Treatment

Cost-effectiveness estimates of IA vary widely, from just over €500 to greater than £412,000 per QALY gained. Estimates indicating cost-effectiveness are generally specific to a particular population and regimen, however the broader and more comprehensive analyses indicate that analogue insulins appear to lack cost-effectiveness.

Recent reviews of the potential link between IA use and cancer raise a number of methodological and statistical questions and indicate that further evidence is required before firm conclusions can be drawn.

There remains a lack of evidence addressing longer-term outcomes of diabetes such as mortality and long-term complications. Given the lack of clear benefits for IA for glycaemic control as well as the inconsistent and clinically debatable benefits for occurrence of hypoglycaemia, along with concerns about trial quality, the current evidence does not indicate a strong advantage for IA compared to RHI for both T1D and T2D.

World Health Organization refused to add IA to the list of essential medications already 2 times. Thus, in 2011 it was stated that with types 1 and 2 of diabetes mellitus, rapid and long-acting insulin analogues do not show pronounced advantages compared to human insulin against the background of scattered statistical data on the positive properties and the absence of clinically significant advantages. It has not been proven that analog insulins are cost-effective, and uncertainty remains regarding the relationship between analog insulins and an increased risk of cancer. An expert committee noted a lack of data on the benefits of insulin analogues over human insulins. The committee evaluated the available data regarding the effect of insulin analogues on the A1c reduction rate and the incidence of hypoglycemia as modest and not justifying the current significant price difference between analogues and human insulins. Based on this assessment, the Expert Committee did not recommend the addition of long-acting insulin analogues as a pharmacological class to the main list of essential medicines for the treatment of type 1 diabetes in adults, adolescents, and children aged 2 years and older [8]. Almost the same story repeated in 2017 [1]. An expert committee noted a lack of data on the benefits of insulin analogues over human insulins. The committee evaluated the available data regarding the effect of insulin analogues on the A1c reduction rate and the incidence of hypoglycemia as modest and not justifying the current significant price difference between analogues and human insulins. Based on

this assessment, the Expert Committee did not recommend the addition of long-acting insulin analogues as a pharmacological class to the main list of essential medicines for the treatment of type 1 diabetes in adults, adolescents, and children aged 2 years and older.The cost-effectiveness of IA depends on the type of IA and whether the patient receiving the treatment has T1D or T2D. With the exception of rapid-acting IA in T1D, routine use of IA, especially long-acting ones in T2D, is unlikely to represent an efficient use of finite health care resources [13].

According to NHS report of prescribing IA over the 10-year period (from 2000 to 2009), the NHS spent a total of £2732 million on insulin (cost was adjusted for inflation and reported in UK pounds at 2010 prices). The total annual cost increased from £156 million to £359 million, an increase of 130%. The annual cost of IA increased from £18.2 million (12% of total insulin cost) to £305 million (85% of total insulin cost), whereas the cost of RHI decreased from £131 million (84% of total insulin cost) to £51 million (14% of total insulin cost). If it is assumed that all patients using IA could have received RHI instead, the overall incremental cost of IA was £625 million.

This investigation concluded, that given the high marginal cost of IA, adherence to prescribing guidelines recommending the preferential use of RHI would have resulted in considerable financial savings over the period.

The case of Great Britain is widely known, in which the cost of insulin therapy for patients with type 2 diabetes increased 3 times during the period 1997-2007, mainly due to the use of expensive insulin analogues. However, an improvement in HbA1c level was achieved only at the level of -0.1% (8.5 - 8.4%). In the event that within 5 years, 50% of people received human insulin instead of insulin analogues, it would be possible to additionally employ 400 doctors or 1,000 specialized diabetic nurses. The experience of insulin therapy in the UK shows that the clinical benefits of insulin analogues do not correlate with their high price, there are no obvious clinical advantages of using insulin analogues in most patients. Given the high cost of insulin analogues, compliance with guidelines recommending the predominant use of human insulin would lead to significant financial savings over this period [11]. Apparently, thanks to such an objective analysis, the current British recommendations do not contain such direct recommendations for the appointment of insulin analogues for type 2 diabetes, as recommendations from other countries. In Germany, IQ WiG, Germany's leading quality control organization, concluded that insulin analogues (rapid and long-acting) have no advantages over human insulins, and therefore the cost difference between insulin analogues and human insulin is assessed as unacceptable.

In 2006, G-BA, the Joint Federal Committee (Decision Center in German Health Care), decided not to finance the use of rapid acting insulin analogues for type 2 diabetes. This has led to a reduction in the cost of these drugs to the level of human insulin. In 2009 and 2010, G-BA decided not to compensate for the cost of long-term analogues for people with type 2 and type 1 diabetes mellitus and short-term insulin analogues for people with type 1 diabetes mellitus until their price is reduced to the price of human insulin. It was decided that reimbursement should be continued only in case of allergy to human insulin and at high risk of severe hypoglycemia [27-30,12]. The results of a meta-analysis of efficacy and safety of IA for the management of diabetes mellitus indicate that IA offer few clinical advantages over conventional insulins in the management of most patients with T1D, T2D or gestational diabetes. Although the evidence supporting the benefit of IA in terms of hypoglycemia is weak, these agents may be an option for patients with problematic hypoglycemia despite optimization of conventional insulin therapy. In a companion paper (see page 369 of this issue), we report on the cost-effectiveness of IA in the management of T1D and T2D in adults. The results of the cost-effectiveness analysis serve to clarify further the optimal place of IA relative to conventional insulins in the management of diabetes in the Canadian health care system.

DISCUSSION

Using the above data, the authors urge all participants in the diabetes market to think about optimizing the cost of helping people who need insulin. The increase in costs due to the increase in the cost of insulin therapy has long resembled a snowball. Such a development of situation insistently tells us that effective program policies are needed to optimize costs on the one hand, and increase the ubiquitous availability of insulin, on the other hand. These two interrelated processes along with the prevention of the development of diabetes mellitus and its complications, including due to the popularization of non-drug approaches [healthy eating, physical activity as a way of life, smoking cessation and minimization of the influence of other modifiable risk factors] should become cornerstones of helping people with diabetes.

Another mandatory approach should be the analysis of the long-term use of different types of insulin, first of all, insulin analogues in comparison with human insulins in terms of the development of late complications of diabetes. The last radical paradigm shift in insulin therapy-the abandonment of the use of animal insulin - has led to at least an almost complete disappearance of the complications of insulin therapy. What changes do we expect thanks to the massive abandonment of human isulin in favor of insulin analogues? By what parameters does the scientific community plan to evaluate the effectiveness of this step.

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