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**ABSTRACT** Despite their reported benefits in terms of glycaemic control, insulin analogues are expensive for patients in developing countries. This study in Jordan aimed to compare the effectiveness and adverse events of premixed human insulin (BHI30) versus premixed insulin analogue (BIAsp30) in patients with type 2 diabetes. In a retrospective cohort study from October 2012 to March 2013, outcomes (HbA1c, weight, hypoglycaemia and lipohypertrophy) were compared at baseline and 6 months after treatment in 628 patients. BHI30 produced a significantly greater reduction in HbA1c than did BIAsp30. This difference in HbA1c remained significant after controlling for the effects of age, sex, duration of diabetes, body mass index and hypoglycaemia (β-coefficient was –0.18 in favour of BHI30). Weight gain and mild hypoglycaemia was significantly higher with BHI30 than with BIAsp30. BHI30 achieved better reduction in HbA1c compared with BIAsp30, with less cost, slightly more weight gain and greater reported mild hypoglycaemia.

## Les analogues de l’insuline sont-ils une nécessité inévitable pour le traitement du diabète de type 2 dans les pays en développement ? Le cas de la Jordanie

**RÉSUMÉ** En dépit des avantages rapportés en termes de contrôle de la glycémie, les analogues de l’insuline sont coûteux pour les patients des pays en développement. La présente étude en Jordanie visait à comparer l’efficacité de l’insuline humaine prémélangée (BHI30) à celle de l’analogue de l’insuline prémélangé (BIAsp30) ainsi que les événements indésirables pour deux substances chez des patients atteints de diabète de type 2. Dans une étude de cohorte rétrospective menée d’octobre 2012 à mars 2013, les résultats (l’hémoglobine glycosylée1c, le poids, l’hypoglycémie et la lipohypertrophie) ont été comparés au début de l’étude, puis six mois après le traitement chez 628 patients. Le traitement par BHI30 a entraîné une réduction très supérieure de l'HbA1c par rapport au BIAsp30. Cette différence dans le taux d'HbA1c est restée importante après la correction pour les effets de l’âge, du sexe du patient et de la durée du diabète, de l’indice de masse corporelle et de l’hypoglycémie (le coefficient-β était de – 0,18 en faveur du BHI30). La prise de poids et l’hypoglycémie légère étaient nettement supérieures sous BHI30 que sous BIAsp30. Le traitement par BHI30 a permis une réduction plus importante de l’HbA1c par rapport au traitement par BIAsp30, à un coût moindre, avec une prise de poids légèrement supérieure et un taux d’hypoglycémie légère plus important.

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## Introduction

Insulin has proven to be the most effective anti-diabetic agent in the past century. The United Kingdom Prospective Diabetes Study showed that beta-cell failure is progressive; 53% of patients with type 2 diabetes mellitus initially treated with sulfonylurea required insulin therapy after 6 years and about 80% required insulin after 9 years (1–3). Previous studies have concluded that the risk of onset and progression of diabetes-related complications such as retinopathy, nephropathy, neuropathy, cardiovascular disease and stroke can be considerably reduced once a sustained reduction of glycosylated haemoglobin (HbA1c) is achieved (4,5). These observations show the importance of intensive and strict glycaemic control starting at the

time of diagnosis of diabetes.

Although most clinical trials demonstrate at least equivalent efficacy of analogues relative to human insulin, with additional benefits in terms of better postprandial glycaemic control, flexible injection timing and improvement in adherence (6–10), many of these trials did not consider the ethnic variations and the difference in eating habits of the study population. For instance, people in the Middle East, including Jordanians, usually have 3 main meals a day, with a relatively high calorie intake at lunch. For this reason conventional insulin administration twice a day—in the morning and evening—will not result in adequate glycaemic control and may indicate the necessity of a third dose before lunch to improve postprandial glucose and HbA1c levels. On the other hand, insulin analogues incur a considerably greater financial cost in comparison with human insulin. This study aimed to show whether insulin analogues could be an unavoidable necessity for the treatment of diabetes mellitus in developing countries such as Jordan.

Jordan is considered one of the smallest economies in the Middle East. The country is very poor in natural resources such as oil, gas and water. The recent waves of migrants and asylum-seekers from neighbouring countries to Jordan have put additional economic and social burdens on Jordan's economy. According to 2012 official figures, the country faces chronic and increasing levels of budget deficit (11.4%), unemployment (12.2%), inflation rate (4.7%) and poverty (11). Furthermore, the public debt increases every year and has reached more than 65% of the country's total gross domestic product. The purchasing power of Jordanian citizens is declining. In addition, the average annual income in 2012 was US$ 4850 and therefore two-thirds of diabetic patients in Jordan could not perform even a single daily testing of blood sugar, given that a single pack of the glucose strips costs around US$ 35. This implies that the patient needs around 1 pack every 17 days and 21 packs every year. The cost of these packs constitutes 15% of Jordanians' average annual income. The cost of insulin, whether human or analogue, is another critical factor. As will be shown later in this paper, the cost of BHI30 is around US$ 31 per month and that of BIAsp30 is around US$ 75 per month. The difference in cost between these 2 alternatives is US$ 525 per patient per year, accounting for an additional 10% of a Jordanian citizen's annual income. These figures sound huge, and necessitate seeking other, less expensive, alternatives. We believe that the cost issue is not unique to Jordan, but a major concern for many other low- and middle-income countries.

The objectives of this study were to compare the effectiveness of premixed human insulin (BHI30) with premixed insulin analogue (BIAsp30) on the reduction of HbA1c in patients with type 2 diabetes mellitus; and to identify the extent of certain adverse events related to the use of human and insulin analogues, such as weight gain, hypoglycaemia and lipohypertrophy.

## Methods

### Sampling

A retrospective cohort study was carried out at the National Centre for Diabetes Endocrinology and Genetics in Amman, Jordan, during the period from 1 October 2012 to 1 March 2013. The study was approved by the Centre's ethics committee. Information was kept strictly confidential and the data were used only for the purposes of this study.

A list of all patients who had their prescriptions of BHI30 or BIAsp30 insulin dispensed from the Centre's pharmacy during the year 2011 was obtained electronically. In our study both BHI30 and BIAsp30 were administered 3 times daily and all patients received metformin treatment as long as the glomerular filtration rate allowed.

The medical files of those patients were reviewed and all patients who were 18 years old or older, had started BHI30 or BIAsp30 insulin at the Centre and had continued on this medication for at least 6 months were eligible to be included in the study. Pregnant women, those in stage 4 and 5 renal failure, with chronic use of steroid medications and poorly compliant patients were excluded from the study. A total of 628 patients (327 on BHI30 and 301 on BIAsp30) were included in the study.

### Data collection

The standard of care at our Centre requires regular follow-up visits for diabetic patients every 2–3 months and all patients receive metformin as long as glomerular filtration rate allows. Routine measurements of blood sugar, HbA1c, blood pressure, weight, waist circumference, urine examination for microalbuminurea, foot screening and fundoscopy are carried out on each visit. Patients on insulin therapy are usually asked about the presence of mild, moderate or severe hypoglycaemia and are screened for lipohypertrophy at insulin injection sites by a diabetic educator nurse. There is no specific rule in prescribing insulin, whether human or analogue; the decision is left to the physician's preference and experience.

Information gathered from the medical records included: baseline data (date of starting BHI30 or BIAsp30 insulin, age, sex, occupation, smoking status, duration of diabetes, weight, height, waist circumference, systolic and diastolic blood pressure, hypertension medication, and HbA1c) and follow-up data at 6 months (weight, HbA1c, and information regarding certain adverse events of insulin treatment such as hypoglycaemia and lipohypertrophy).

#### Definitions

Diabetes was considered to be controlled if the patient had HbA1C level 0.5 (13). Body mass index (BMI) was expressed as the quotient between weight (kg) and height squared (m2). Patients with BMI of 30 kg/m2 or more were considered obese (14). Weight difference was the difference between weight at the starting date of insulin therapy and the value at the end of the 6-month period.

Hypertension was defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg or if the patient was on antihypertensive drugs (12).

Metabolic abnormalities were defined according to the American Diabetes Association 2011 guidelines (12) as follows: total serum cholesterol ≥ 200 mg/dL (5.17 mmol/L), serum low-density lipoprotein cholesterol ≥ 100 mg/dL (2.59 mmol/L), serum triglyceride ≥ 150 mg/dL (1.70 mmol/L), serum high-density lipoprotein cholesterol ≤ 40 mg/dL (1.03 mmol/L) in men, and ≤ 50 mg/dL (1.29 mmol/L) in women, or if the patient was already on antidyslipidaemic agents.

Smoking was classified into non-smoker (never smoked), past smoker (used to smoke but stopped smoking) and current smoker (smoked cigarettes daily or occasionally) (15).

### Statistical analysis

Analysis was carried out using SPSS, version 17. A P-value ≤ 0.05 was considered statistically significant. Frequency and percentage distribution was used for categorical variables, and means and standard deviations (SD) for continuous variables. Independent t-test was used to test for a significant difference of mean HbA1c difference and mean weight change in patients taking premixed human (BHI30) versus premixed insulin analogue (BIAsp30). Pearson chi-squared test was used to determine the significant difference of hypoglycaemia, lipohypertrophy and HbA1c control in patients taking premixed human (BHI30) versus premixed insulin analogue (BIAsp30). Multiple linear regression analysis was performed to examine the net effect of the mentioned types of insulin on mean difference of HbA1c after controlling for the effect of potential confounders.

## Results

### Participants' characteristics

A total of 628 patients with type 2 diabetes were studied: 301 on BIAsp30 and 327 on BHI30. As indicated in Table 1 and Table 2 , the 2 groups were comparable on most of the sociodemographic and health characteristics; however, the mean baseline HbA1c value was significantly higher among BHI30 users ( Table 2 ).

Comparison of HbA1c and weight change, hypoglycaemia and lipohypertrophy between insulin groups

After 6 months of treatment with BHI30 insulin, the mean HbA1c dropped from 10.7% (SD 1.8%) to 8.6% (SD 1.6%), a decrease of 2.1% (SD 2.1%), while with BIAsp30 treatment HbA1c dropped from 9.7% (SD 1.7%) to 8.5% (SD 1.5%), a decrease of 1.2% (SD 1.7%). This difference between the BHI30 and BIAsp30 groups in terms of the decrease of mean HbA1c level was statistically significant (P Table 3).

The baseline mean weight in the BHI30 was 83.7 (SD 16.5) kg and this increased to 86.8 (SD 15.6) kg after 6 months, a mean increase of 3.1 (SD 4.3) kg. In the BIAsp30-treated group the mean weight increased from 85.4 (SD 17.4) kg to 87.5 (SD 17.3) kg, a mean increase of 21. (SD 3.8) kg ( Table 3 ). The mean difference in weight change between the 2 groups [1.0 (SD 0.3) kg]was statistically significant (P = 0.002) ( Table 3 ).

During the treatment period, the percentage of patients who reported hypoglycaemia with BHI30 treatment was 29.7% compared with only 17.4% in the BIAsp30-treated group (P