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Efficacy and Safety of Berberine for Prediabetes: A Systematic Evaluation and Meta-Analysis

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Abstract

Objective: To assess the efficacy and safety of berberine in the treatment of prediabetes. **Methods:** We searched the following databases, CNKI, Wan-Fang, VIP, CBM, PubMed, Cochrane Library, Embase, and Medline (OVID) from the databases established to December 2020 in Chinese or English language. Randomized control trials (RCTs) of berberine compared with lifestyle modification, placebo, and/or hypoglycaemics intervention on treating prediabetes were included. Data extraction and paper quality assessment were conducted according to the Cochrane Handbook. RevMan 5.4 was used for the meta-analysis. **Results:** Seven studies involving 859 participants were included in the study and the control groups were all lifestyle modification or metformin treatment. The clinical heterogeneity of the trials was relatively high, and the methodological quality of most trials was generally low. Meta-analysis suggested that berberine could reduce FPG ($P = 0.001$), 2hPG ($P = 0.001$) and HbA1c ($P = 0.002$) levels significantly as compared with lifestyle group. There was no statistical significance between berberine and metformin. No serious adverse effects from berberine were reported. **Conclusions:** Berberine has good efficacy and safety in the treatment of prediabetes. Due to the quality limitations of the included trials, the above conclusions need to be further verified by high-quality, large sample size and multi-center clinical trials.

Keywords

Berberine, Prediabetes, Efficacy, Safety, Meta-Analysis

1. Introduction

Prediabetes refers to the intermediate hyperglycemia state between normal blood

glucose and diabetes [1]. It is also known as impaired glucose regulation (IGR), including impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). The epidemiological survey showed that the prevalence of prediabetes was 35.2% [2]. The prevalence among males and females was 37.0% and 33.4% respectively [2]. Prediabetes is considered the most significant risk factor for type 2 diabetes (T2DM). It is estimated that the world's prediabetic population will grow to 470 million by 2030 [3], and about 70% of them will develop diabetes at some point [4]. The damages of hyperglycemia already exist before diabetes. So prediabetes is considered a marker or watershed, which means that the risk of cardiavascular disease, diabetes, microangiopathy, tumor, and dementia will increase in the future [5]. But the blood sugar can be reversed to normal after appropriate treatment. At Present, prediabetic patients mainly depend on lifestyle interventions to prevent or delay diabetes. It is generally considered to be safe and cost-effective. However, only a small number of patients can adhere to their diatary plans and exercise prescriptions and it is reported that about 10% - 20% of prediabetic patients are resistant to the effects of exercise with weight loss [6]. A six-year follow-up study showed that about 50% of the prediabetic patients who had received lifestyle interventions still developed diabetes [7]. Therefore, the guidelines recommend if no satisfactory results are achieved after six months of active interventions, metformin or acarbose should be considered [5]. For young patients having solid financial support and strong health needs, early pharmaceutical interventions are highly recommended [8]. But the high cost and side effects of western medician limit the clinical application. So it becomes increasingly important to develop cost-effective safe hypoglycemic drugs.

Prediabetes belongs to the "spleen" of traditional Chinese medicine (TCM), which is the philosophy of corrective and preventative action against disease [9] [10]. Berberine (BBR, molecular formula: C20H19NO5, molecular weight: 353.36) is a natural alkaloid extracted from the rhizome of Chinese goldthread (Coptis chinensis) and Phellodendron bark (Cortex phellodendri) [11] and is well known as the effective drug that can relieve the symptoms of infectious diarrhea. Modern pharmacological studies have confirmed that berberine has significant hypoglycemic and lipid-regulating effects, improving insulin resistance and anti-inflammatory effects [12] [13] [14]. Some clinical trials have also confirmed berberine has the same hypoglycemic effect on prediabetes. But no one has done a systematic evaluation for it. This research used the Cochrane systematic evaluation method and evaluated the efficacy and safety of berberine in treating prediabetes in RCTs. This can provide a critical reference for clinical decision-making.

2. Materials and Methods

2.1. Search Strategy

We searched the China National Knowledge Infrastructure (CNKI), the Wan-

Fang Database, the Chinese Scientific Journal Database (VIP), the Chinese Bio-Medical Literature Database (CBM), PubMed, Cochrane Library, Embase, and Medline (OVID) from the databases established to December 2020 in any language. Ongoing trials reported by ClinicalTrials.gov were also searched. The following search terms were used: ["Berberine" or "Huangliansu" or "Xiaopojian"] and ["prediabetes" or "pre-diabetes" or "impaired glucose tolerance" or "impaired fasting glucose" or "impaired glucose regulation"]. In addition, the reference lists from articles were manually searched for further studies.

2.2. Inclusion Criteria

Studies were included if they fulfilled the following criteria: design of parallel RCT of berberine intervention compared with lifestyle modification, placebo, and/or hypoglycaemics on treating prediabetes, whether allocation concealment and blinding were used or not; Literature is either Chinese or English literature. Some studies contained multiple groups and each comparison group containing berberine was considered as a separate trail in the analysis. Studies were only included if the intervention was given for at least 2 months. Prediabetes was diagnosed by internationally recognized criteria. No sex or age limitation. The diagnosis criteria include WHO 1999 [15], CDS 2013 [16] and ADA 2010 [17].

The primary outcomes consisted of fasting plasma glucose levels (FPG), 2-hour postprandial plasma glucose (2hPG), glycosylated haemoglobin levels A1c (HbA1c) and homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β cell function (HOMA-β). The secondary outcomes consisted of body mass index (BMI) and adverse effects.

2.3. Exclusion Criteria

The exclusion criteria were non-randomized controlled trials and quasi-randomized control trials; abstracts or comments from conference papers; animal studies or comparative studies on different Chinese medicine therapies.

2.4. Data Extraction

Literature selecting: read the article title and abstract, eliminated the studies not meeting the inclusion/exclusion criteria. Two reviewers independently assessed trials for inclusion in the review. They extracted data concerning details of the sample size, interventions, duration of treatment, and outcomes by using a standard Microsoft Excel (Microsoft Corporation, office 2016) file. Any disagreements were resolved by consensus, or if required by a third reviewer.

2.5. Quality Assessment

The quality of the included trials was assessed using the Cochrane risk bias tools (Review Manager 5.4 provided by the Cochrane Collaboration) [18]. The criteria include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome

data, selective reporting and other bias. We made judgement on each of these criteria relating to the risk of bias: low, high, or unclear (indicating unclear or unknown risk of bias).

2.6. Statistical Methods

We used the RevMan 5.4 meta-analysis software to summarize the effects of berberine. Categorical variables used odds ratio (OR) and continuous variables used the mean differences (MD) as analysis statistics. 95% confidence interval (95% CI) was used as the effective size for the combined analysis. The clinical and methodological heterogeneity of the included studies was evaluated with X^2 test and I^2 test. The different berberine interventions and control methods were used for sensitivity subgroup analysis. Reporting bias was explored through funnel plot analysis when the number of included trials exceeded ten. A fixed-effect model was used when the studies in the subgroup were sufficiently similar ($I^2 <$ 50%, $P > 0.10$). Otherwise, a random-effect model was used. When $P < 0.05$, it indicated that there was a significant difference between the two groups. Interval estimation and hypothesis test results were shown in the forest plot.

3. Results

3.1. Literature Search Results

The flowchart of study search results is displayed in **Figure 1**. The primary searches identified a total of 364 references. 153 articles were screened after 211 duplicates of the same articles were removed. According to the inclusion criteria, 146 records were excluded because they were animal studies, not prediabetes, not RCTs, reviews or comments. Finally, seven studies met the eligibility criteria and were included in the systematic review and meta-analysis.

3.2. Characteristics of the Included Studies

The seven studies, including six in Chinese and one in English, were published in 2007-2020. All the studies were performed as single center trials and originated from the mainland of China. Six studies [19] [20] [22] [23] [24] [25] adopted two-armed paralled group design. One study [21] adopted three-armed group design, including berberine, lifesyle modification and metformin. One study [23] set a washout period between two treatment periods of berberine vs. lifestyle modification. According to the inclusion criteria, the two studies [21] [23] were analyzed as four trials. A total of 859 prediabetic patients were enrolled. Among them, 431 were in the experimental group and 428 in the control. The baseline consistency of each trial was comparable. See **Table 1**.

3.3. Risk of Bias in Included Studies

We used RevMan 5.4 to assess the risk of bias in included seven studies. None of them reported the research plan and sample size estimation method. All the studies mentioned random assignment of participants. But only two studies described

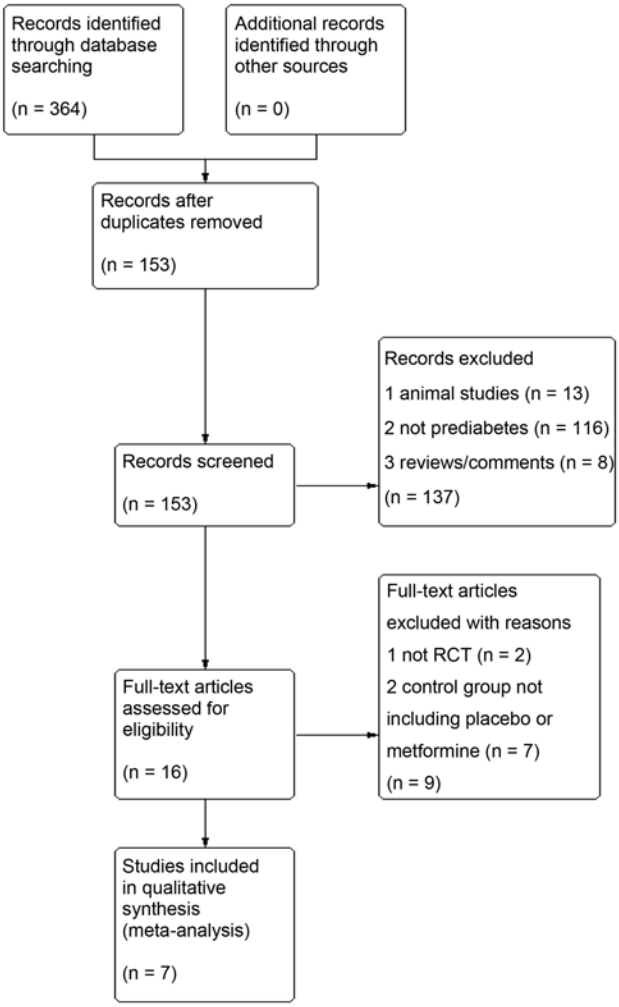

Figure 1. Flow chart of the strategy used for the selection of studies used in the meta-analysis.

Table 1. Characteristics of the included trials.

Study	Number of patients (Man/Female)		Intervation		Duration (month)	Outcomes
	Experimental	Control	Experimental	Control		
Ju SB 2007 [19]	46 (28/18)	44 (26/18)	BBR 0.6/d + LM	LM	12	①②③④⑥
Zhang ZJ 2018 [20]	50 (27/23)	50 (32/18)	BBR 0.3 tid + LM	LM	4	①⑥⑦
Chang HY 2020 (1) [21]	80 (45/35)	80 (42/38)	BBR 30 mg tid	LM	6	①②③④⑥⑦
Chang HY 2020 (2) [21]	80 (45/35)	80 (41/39)	BBR 30 mg tid	Met 0.25 tid → 0.5 tid	6	①②③④⑥⑦
Zhang Z 2020 [22]	24 (-/-)	24 (-/-)	BBR 0.2 tid + LM	LM	2	⑥
Wang L 2020 (1) [23]	35 (19/16)	35 (19/16)	BBR 0.3 tid + LM	LM	3	①②③④⑦
Wang L 2020 (2) [23]	34 (19/15)	33 (18/15)	BBR 0.3 tid + LM	LM	3	①②③④⑦
Zhao JQ 2018 [24]	32 (26/6)	32 (24/8)	BBR 0.3 tid + LM	LM	3	①②③⑥
Chen YM 2017 [25]	50 (31/19)	50 (30/20)	BBR 0.5 tid	Met 0.25 tid	6	①②⑥

Note: -, no record; BBR, berberine; LM, lifestyle modification; Met, metformin; ① FPG; ② 2hPG; ③ HbA1c; ④ HOMA-IR; ⑤ HOMA-β; ⑥ BMI; ⑦ adverse effects.

random sequence generation methods, such as random number tables [20] [23]. There was insufficient information to determine whether the randomizations were carried out correctly in the rest of the studies. Only one study described the allocation concealment [22], one study used a single blind [22], and three studies reported the number of withdrawals and drop-outs in each group [19] [22] [23]. None of the studies indicated any other bias. The risk of bias in included studies is shown in **Figure 2**.

3.4. Outcome Indicators

Seven studies (nine trials) were included in the study. The control groups were all lifestyle modification or metformin treatment. Considering that the intervention measures of berberine treatment are different, the influencing factors such as drug dosage and course of treatment can not be combined and analyzed. Therefore, the intervention types of experimental and control groups were analyzed in subgroups, which were divided into berberine vs. lifestyle and berberine vs. metformin. Because some data in Wang L [23] article, our previous research results, were abnormal distribution, the meta analysis was carried out on the basis of the original data.

3.4.1. Efficacy of Berberine Treatment on FPG

There were six trials that compared the effect of berberine vs. lifestyle on FPG and two trials for berberine vs. metformin. Due to high heterogeneity, $I^2 > 50\%$, random-effect (RE) model was used for the analysis. Subgroup analysis showed that berberine significantly reduced FPG level compared with lifestyle group, [MD = −0.39, 95% CI (−0.63, −0.16), $P = 0.001$]. There was no significant difference between berberine and metformin, [MD = −0.01, 95% CI (−0.08, 0.05), $P = 0.71$]. See **Figure 3**.

3.4.2. Efficacy of Berberine Treatment on 2hPG

There were six trials that compared the effect of berberine vs. lifestyle on 2hPG and two trials for berberine vs. metformin. Due to high heterogeneity, $I^2 > 50\%$, random-effect (RE) model was used for the analysis. Subgroup analysis showed

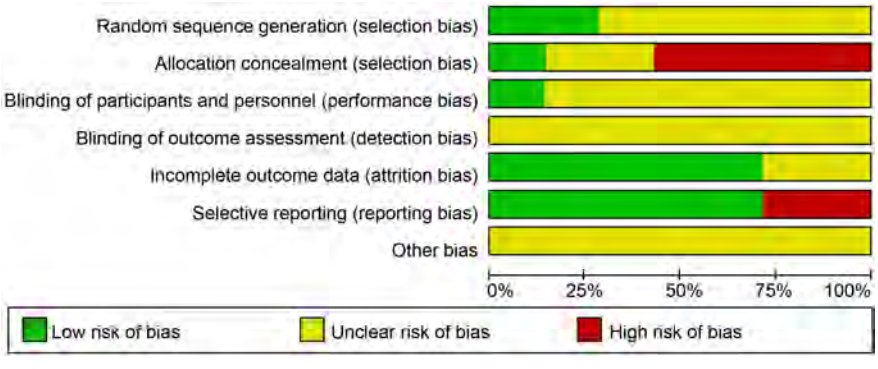

Figure 2. Risk of bias accessed using RevMan 5.4 according to the guidance in the Cochrane Handbook. Green represents low risk of bias, yellow represents unclear risk of bias, and red represents high risk of bias.

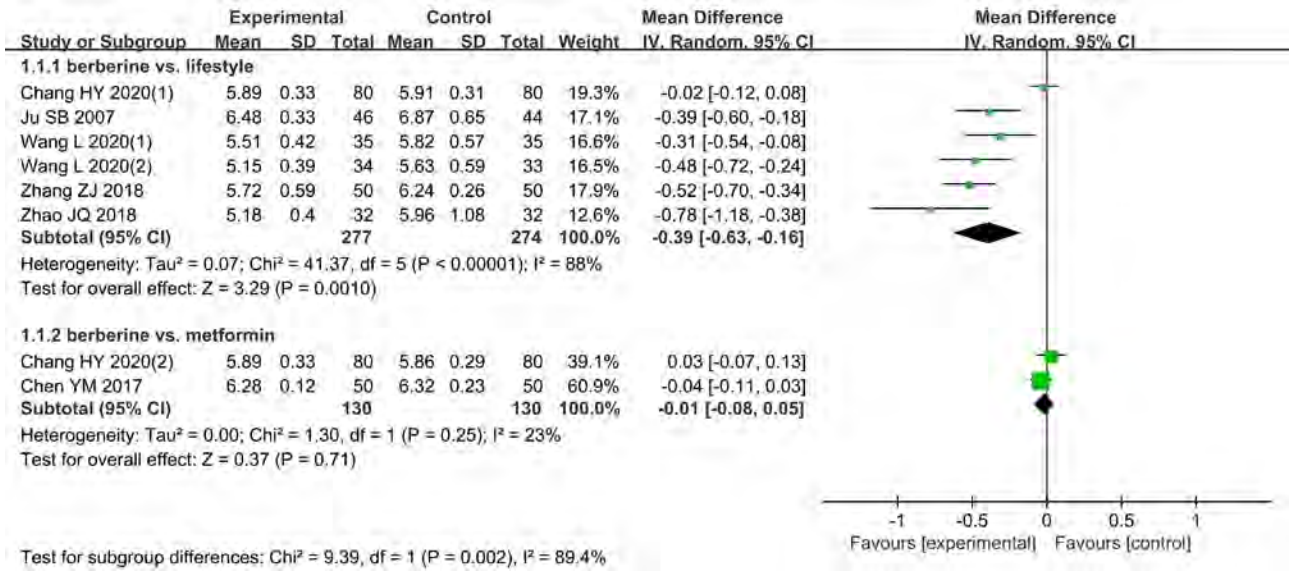

Figure 3. Forest plot of outcome measure FPG.

that berberine significantly reduced 2hPG leval compared with lifestyle group, [MD = −1.51, 95% CI (−2.43, −0.59), P = 0.001]. There was no significant difference between berberine and metformin, [MD = −0.07, 95% CI (−0.29, 0.14), P = 0.51]. See **Figure 4**.

3.4.3. Efficacy of Berberine Treatment on HbA1c

There were six trials that compared the effect of berberine vs. lifestyle on HbA1c and two trials for berberine vs. metformin. Due to high heterogeneity, I^2 > 50%, random-effect (RE) model was used for the analysis. Subgroup analysis showed that berberine significantly reduced HbA1c level compared with lifestyle group, [MD = −0.20, 95% CI (−0.32, −0.08), P = 0.002]. There was no significant difference between berberine and metformin, [MD = −0.03, 95% CI (−0.08, 0.02), P = 0.22]. See **Figure 5**.

3.4.4. Efficacy of Berberine Treatment on HOMA-IR

There were four trials that compared the effect of berberine vs. Lifestyle on HOMA-IR and one trial for berberine vs. metformin. Due to high heterogeneity, I^2 > 50%, random-effect (RE) model was used for the analysis. There was no significant difference between berberine and lifestyle or metformin, [MD = −0.13, 95% CI (−0.33, 0.06), P = 0.18] and [MD = −0.01, 95% CI (−0.05, 0.03), P = 0.64], respectively. See **Figure 6**.

3.4.5. Efficacy of Berberine Treatment on HOMA-β

One trial compared the effect of berberine vs. lifestyle on HOMA-β. There was no significant difference between the two groups, [MD = 0.17, 95% CI (−0.03, 0.37), P = 0.09]. See **Figure 7**.

3.4.6. Efficacy of Berberine Treatment on BMI

There were four trials that compared the effect of berberine vs. lifestyle on BMI

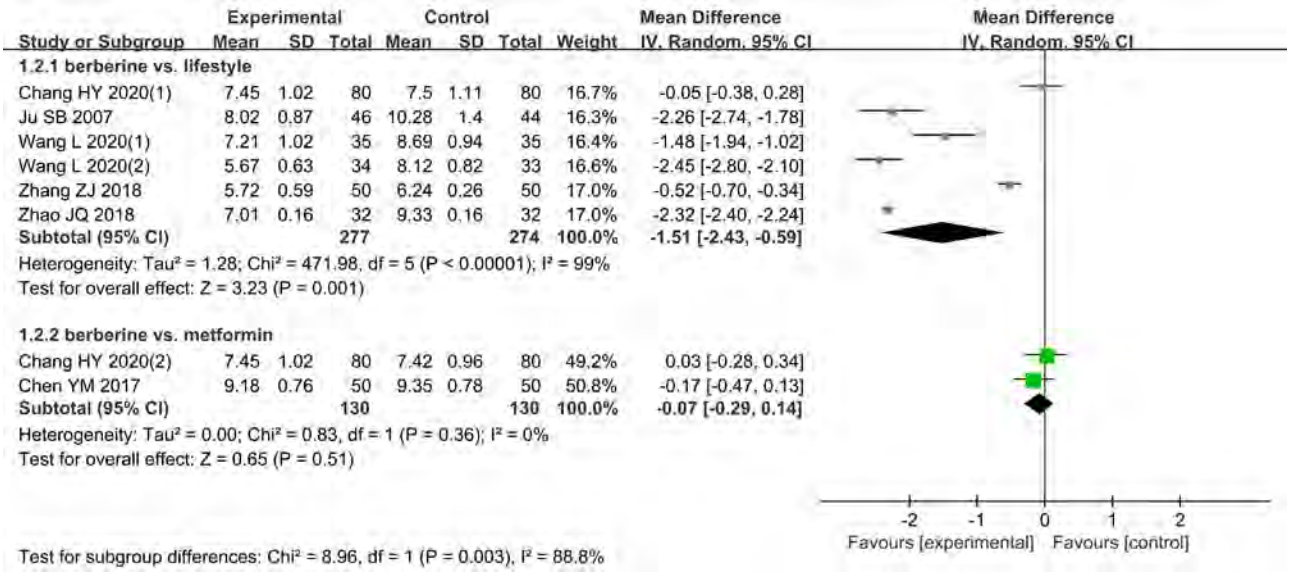

Figure 4. Forest plot of outcome measure 2hPG.

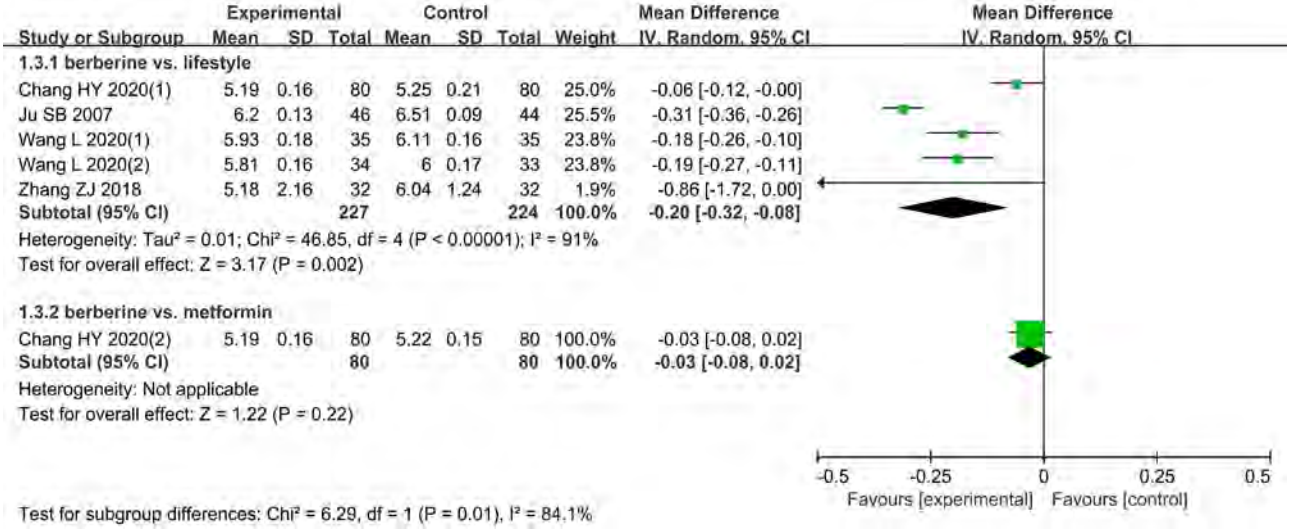

Figure 5. Forest plot of outcome measure HbA1c.

and one trial for berberine vs. metformin. Due to high heterogenerty, $I^2 > 50\%$, random-effect (RE) model was used for the analysis. There was no significant difference between berberine and lifestyle or metformin, [MD = −1.14, 95% CI (−2.52, 0.25), $P = 0.11$] and [MD = −0.45, 95% CI (−1.63, 0.73), $P = 0.45$], respectively. See Figure 8.

3.4.7. Efficacy of Berberine Treatment on Adverse Effects

Five trials reported the number of adverse effects and the other trials only stated slight adverse effects of berberine without clear data. Due to low heterogeneity, $I^2 < 50\%$, fixed-effect (FE) model was used for the analysis. Subgroup analysis showed that there was no significant difference between berberine and lifestlye, [MD = 3.75, 95% CI (0.61, 23.2), $P = 0.15$]. Compared with metformin, the

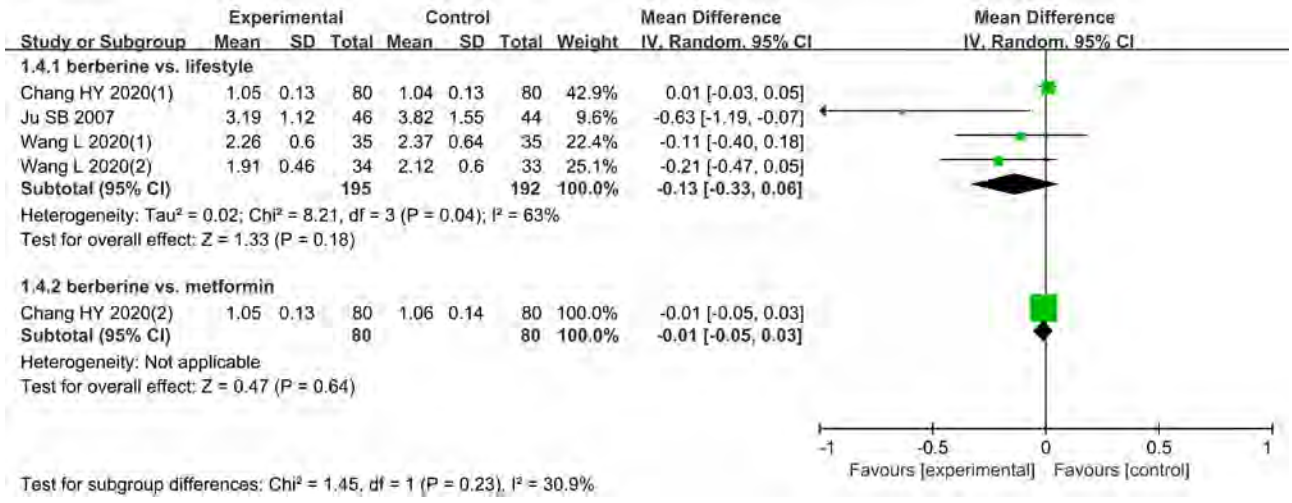

Figure 6. Forest plot of outcome measure HOMA-IR.

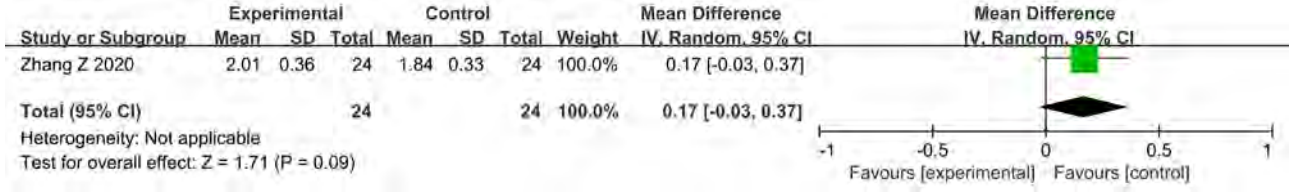

Figure 7. Forest plot of outcome measure HOMA-β.

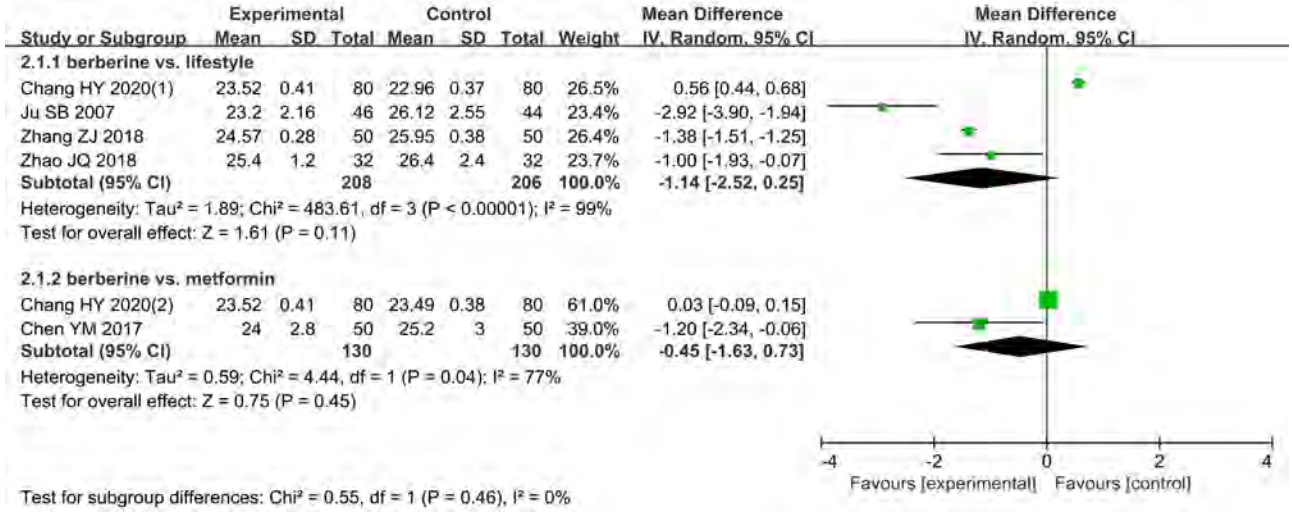

Figure 8. Forest plot of outcome measure BMI.

adverse effects rate of berberine was significantly decreased, [MD = 0.11, 95% CI (0.01, 0.93), $P = 0.04$]. All reported events were mild, including constipation, diarrhea, nausea and abdominal distension. No serious adverse effects from berberine were reported. See **Figure 9**.

3.5. Sensitivity Analysis

Sensitivity analysis was carried out by eliminating literature one by one. FPG,

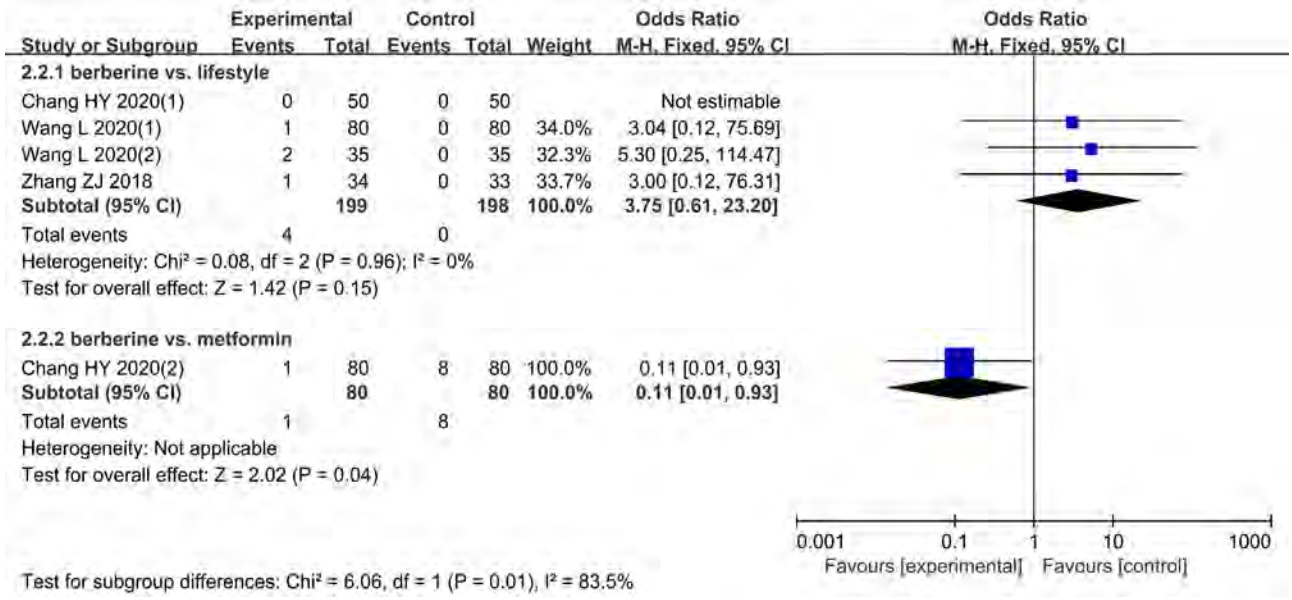

Figure 9. Forest plot of adverse effects.

HOMA-IR and BMI for the subgroup of berberine vs. Lifestyle, were significantly affected by the article, Chang HY [21]. The results changed from [P = 0.001, I^2 = 88%, MD = −0.39, 95% CI (−0.63, −0.16)], [P = 0.18, I^2 = 63%, MD = −0.13, 95% CI (−0.33, 0.06)] and [P = 0.11, I^2 = 99%, MD = −1.14, 95% CI (−2.52, 0.25)] to [P = 0.00001, I^2 = 19%, MD = −0.46, 95% CI (−0.58, −0.35)], [P = 0.04, I^2 = 23%, MD = −0.23, 95% CI (−0.44, −0.01)] and [P = 0.0002, I^2 = 80%, MD = −1.71, 95% CI (−2.60, −0.81)], respectively. After excluding the article, berberine could also significantly reduce HOMA-IR and BMI of prediabetes.

3.6. Publication Bias Analysis

Owing to the limited number (below ten) of trials included in each analysis, publication bias was not assessed.

4. Discussion

4.1. Summary and Analysis of Evidence

There have been a lot of clinical studies or reports about berberine in the treatment of T2DM. But it is relatively few studies for prediabetes. At present, no meta-analysis of the efficacy and safety of berberine in prediabetes has been done. In this systematic review, we selected seven clinical studies and the strategy follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A total of 859 participants were involved, of which 431 and 428 were in the experimental and control groups. Our findings upon the seven studies showed that compared with lifestyle group, berberine could lower the level of FPG [MD = −0.39, 95% CI (−0.63, −0.16), P = 0.001], 2hPG [MD = −1.51, 95% CI (−2.43, −0.59), P = 0.001] and HbA1c [MD = −0.20,

95% CI (−0.32, −0.08), $P = 0.002$]. There was no statistical significance between berberine and metformin. In addition, berberine evaluated in our review generally appeared to be safe. The adverse effects were commonly gastrointestinal discomforts including constipation, diarrhea, nausea and abdominal distension. No serious adverse effects from berberine were reported.

In order to minimize the heterogeneity, we used the subgroup analysis according to different interventions. However, when FPG, 2hPG, HbA1c, HOMI-IR and BMI data were aggregated in the subgroup of berberine vs. lifestyle, the heterogeneity was still high. Then we used the method of eliminating references one by one to carry out the sensitivity analysis. It was found that Chang HY, 2020(1) [21] had the greatest impact on the results. Berberine could also significantly reduce HOMA-IR [$P = 0.04$, $I^2 = 23\%$, MD = −0.23, 95% CI (−0.44, −0.01)] and BMI [$P = 0.0002$, $I^2 = 80\%$, MD = −1.71, 95% CI (−2.60, −0.81)] after excluding the article. The reason may be that the doses of berberine in this study were significantly lower than those in other studies.

4.2. limitations

This analysis also has several limitations. All the included studies were conducted among Chinese participants in the mainland of China. There was a high risk of selection bias. Although all the studies mentioned random allocation, five studies did not describe the generation of random sequences, and most of the studies did not describe adequate allocation concealment. Only one study described single blindness. Three studies reported withdrawals and drop-outs. So it may lead to selection bias and implementation bias. Potential bias in selection of patients (such as age, gender or blood glucose level at baseline), administration of treatment and assessment of outcomes could lead to overestimation of the therapeutic efficacy of berberine. Moreover, the research approaches of the trials were not described or published in advance. These may lead to follow-up bias and reporting bias. Owing to the limited number (below ten) of trials included in each analysis, publication bias was not assessed. Therefore all of the outcomes should be carefully interpreted based on substantial methodological and clinical diversity.

4.3. Inspiration

This study suggests that the methodological quality of berberine in the treatment of prediabetes is generally low, which may lower the internal authenticity of the results, then affect their external authenticity. High quality RCTs should be carried out, especially scientific and reasonable methodological research design. Attentions should be paid to the design and implementation of clinical studies: 1) Register programmes prior to implementation; 2) Estimate sample size before the study; 3) Report detailedly on random sequence generation, allocation concealment and blinding of participants, researchers and evaluators; 4) Report results and analyze reasons of withdrawals and drop-outs; 5) Large sample sizes

and long-term follow-up are needed to the evaluation of the efficacy and safety of berberine; 6) Report strictly according to CONSORT [26] to improve the levels of evidence and clinical values.

5. Conclusion

This study indicates that Berberine has good efficacy and safety in the treatment of prediabetes. Due to the quality limitations of the included trials, the above conclusions need to be further verified by high-quality, large sample size and multi-center RCTs.

Conflicts of Interest

None of the authors has any potential conflicts of interest associated with this research.

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Racial Differences Effects on Oral Health and Periodontal Diseases Extent, Staging and Grading among the Multi-Ethnic Expatriates in Aseer Region, Saudi Arabia

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Abstract

Background: Given the increase in the numbers of expatriates in Saudi Arabia and the shortage of information about expatriates' oral health and periodontal disease severity and progression. **Objectives:** This study aimed to evaluate the effects of the racial differences on oral health and periodontal disease extent, staging, and grading among the multi-ethnic expatriates in the Aseer region, Saudi Arabia. **Materials and Methods:** This cross-sectional study was carried out on 300 expatriates in Aseer region, Saudi Arabia. They were divided into three equal racial different groups (n = 100), Arabs (AR), Asians (AS), and Africans (AF). The interviews of all participants were completed then the clinical examinations of periodontal diseases extent, staging, and grading parameters were performed. Statistical analysis was done by ANOVA test, Tukey's test, and Chi-square test. The statistical significance level was determined at $p < 0.05$. **Results:** There were statistically significant differences in the comparison between the three ethnic/racial groups in clinical parameters except in GBI, PCR, FI, TFO, and BC, where there were no statistically significant differences in the comparison between the three ethnic/racial groups. There were differences associated with age, gender, smoking, and diabetes, without statistically significant differences among the three racial groups. **Conclusion:** We concluded that most participants in this study had a generalized severe grade 4 plaque-induced gingivitis and localized periodontitis stage III grade B.

Keywords

Multi-Ethnics, Oral Health, Periodontal Diseases Extent, Staging and Grading

1. Introduction

Oral health is necessary for public health and lifestyle. Consequently, Bad oral health maybe leads to difficulties eating or speaking and restrict daily life [1]. On the other hand, periodontal disease is a multifactorial inflammatory disease of the oral cavity that can be gingivitis confined only to the gingiva or periodontitis when exceeding the soft tissues and affects the hard tissues attachment of the teeth [2]. Periodontal disease affects 10% - 15% of people worldwide. Thus, it has a high effect on general health [3].

Periodontal diseases occur in all age groups due to common etiological and other predisposing factors that, causing the initiation and progression of periodontal diseases [4] [5]. Comparable to other chronic diseases, periodontal disease is considered a complex disease, and patient behaviors, environmental factors, medication use, genetic and epigenetic influences establish periodontal disease development [6]. Periodontitis affecting on 13% to 57% of adult populations in the Arab World, and mild-to-moderate periodontitis is the most common form [7] [8] [9].

The races of patients also promote the individuals' predisposition to periodontal diseases [10]. Racial differences in periodontal diseases in the U.S. have been recognized, with African Americans and Mexican-Americans as more susceptible to periodontal diseases than other racial groups [11] [12], where the periodontal health among white people is better than other ethnic groups [13]. This may be due to the effect of race on income and education [14]. Thus, recognition of racial variations is a significant side to recognizing the people's oral and public health and planning suitable [15].

The self-identification of the races is a complex process that includes several factors: geographical, inherited, ethnic, and somatic characteristics, moreover the language, customs, religion, and culture. The racial groups differ in lifestyle, such as smoking and diet, alcohol consumption also their dental services. As well as the impacts of assimilation, expatriation, and discrimination, furthermore, environmental effects such as variations in personal- and region-based socioeconomic level and the racial blend of people [16] [17]. Former studies display that the racial variations in oral health linked by behavioral, cultural, socioeconomic factors, as well as access to dental services and there were high level of dental diseases and low level of oral care among expatriates in contrast with local-born [18] [19] [20] [21]. There are multi distinct races among the minority groups, and oral health troubles highly spread between them [22].

In Saudi Arabia, 30% of the population is as expatriates from worldwide, and as far as we know, there is no study in the college of dentistry, King Khalid University, that displays the impact of racial differences on oral health and periodontal diseases extent, staging and grading among the multi-ethnic expatriates in Saudi Arabia. Therefore, the purpose of the present study is to evaluate oral health and periodontal status among expatriates from different racial origins in the Aseer region, Saudi Arabia.

2. Materials and Methods

2.1. Design of Study and Sample Size

This retrospective descriptive study was done on 300 expatriate patients with periodontal diseases at the clinics of the college of dentistry, King Khalid University, from 1st of October 2020 to the end of February 2021. The present study comprised three different race groups living in Saudi Arabia as group I (Arabs), group II (Asians), and group III (Africans). The three groups of the present study are all expatriates to Saudi Arabia recently (within the last 20 years). Consequently, they still in close connections with their origin countries, which can help them to resist alter behavior and beliefs. The sample size in the present study was determined to depend on a study conducted by Eke, *et al*. in 2012, a sample size of n = 300 (100 per group) [12].

2.2. Ethical Considerations and Ethics Approval

Written informed consent gained. The participants in the present study were volunteers and received explanations about the nature of the study, then their written informed consent was obtained. Moreover, ethical approval was obtained from the institutional review board, the college of dentistry, King Khalid University (IRB/REG/2020-2021/75).

2.3. Inclusion and Exclusion Criteria

The participants with or without systemic disease are involved in this study. The main inclusion criteria for all participants in the current research that they should be non-Saudi, and they all should be from three different races according to the study design. Study participants without periodontal diseases and who received mechanical and chemical periodontal therapy excluded. We excluded the participants who did not clarify their ethnic group and mixed ethnic group to avoid the difficulty in the interpretation of the results due to the heterogeneity within these groups.

2.4. Participants' Characteristics

In this study, we determine race and gender as non-changeable factors, whereas oral health periodontal parameters, smoking, diabetes are grouped as changeable factors. The participants' characteristics as age, gender, and race were included in our assessment to investigate the effects of these factors on oral health and periodontal diseases extent, staging and grading. We checked the other characteristics of the participants, such as the presence of diabetes and smoking status. The age range of the participants was between 14 - 89 years old.

2.5. Clinical Examination

The participants was interviewed and clinically examined by the researchers on the authority of to World Health Organization's (WHO) criteria [23]. Gingival

bleeding index (GBI), plaque control record (PCR) recorded [24] [25]. Moreover, clinical attachment loss (CAL), percentage (%) of bone loss (%BL), number of teeth missing due to periodontal diseases (NMT), Periodontal pocket depth (PPD), Pattern of bone loss (PBL), tooth mobility (TM), furcation involvement (FI), present of trauma from occlusion (TFO), bite collapse (drifting, flaring) (BC) and less than 20 remaining teeth (10 opposing pairs).

Periodontal disease in the present study was determined, like gingival diseases and periodontitis. Gingival diseases include localized or generalized (mild or moderate or severe), grade 1 or 2 or 3 or 4 or 5 dental plaque-induced gingivitis. Moreover, periodontitis was diagnosed as localized and generalized, stage I, II, III, or IV periodontitis. Diabetic status was determined by the glycated hemoglobin (HbA1c) test. When HbA1c less than 7.0, it will be grade periodontitis grade B, and when HbA1c of 7.0 or more, it will be periodontitis grade C. The participants' smoking status was determined, as smokers and non-smokers. When the participant's smoking less than ten cigarettes daily, it will be, periodontitis grade B, and when the participant's smoking ten cigarettes or more, it will be periodontitis grade C [26] [27].

2.6. Radiographic Evaluation

The alveolar radiographic bone loss in the current study evaluated as percentages of radiographic bone loss where we measured, in millimeters, the distance from the cement-enamel junction (CEJ) to the alveolar bone crest (ABC) as well as the distance from CEJ to the root apex with the calibrated measuring tool of Emago® (Oral Diagnostic Systems, Amsterdam, Netherlands) software—the radiographic imaging software at HSDM. Percentage bone loss is calculated by the difference between those distances multiplied by 100 [28]. The percentage of radiographic bone loss divided by the patient's age applied to the evaluation of periodontitis progression [29] [30].

2.7. Glycosylated Hemoglobin (HbA1c) Assessment

The medical reports of participants were used to identify glycosylated hemoglobin more or less than 7%, and according to these reports, the test kit (A1cNow+) was used with a laboratory method (Ion Exchange Resin method) using a semi-auto analyzer [31].

2.8. Statistical Analysis

The age and clinical parameters of the participants of the three groups were compared using the ANOVA test. Whereas the comparison between group I and II and between III and I. Moreover, a comparison between groups II and III based on their age and clinical parameters conducted using Tukey's test. Chi-square test carried out to the comparison between groups II, III, and I in the participants' characteristics and clinical parameters. The statistical significance level was determined at $P < 0.05$.

3. Results

The present study samples included 300 participants. There were 200 (66.7%) males and 100 (33.3%) females. They were divided into three equal groups Arabs (group I), Asians (group II), and Africans (group III). The ranges of ages for groups I, II&III were 14 - 89 ys, 21 - 76 ys, and 18 - 81 ys with means and standard deviations (±SD) 32.3 ± 14.5 ys, 42.96 ± 12.7 ys, and 39.32 ± 12.9 ys, respectively. Consequently, the ages of Asian participants more than the ages of Arabs and Africans, and the participants' ages of Africans more than the participants' ages of Arabs, and there were highly statistically significant differences in the comparison of the participants' ages between Arabs, Asians and Africans, Arabs and Asians and Arabs and Africans, without statistically significant differences in the comparison of the participants' ages between Asians and Africans (Table 1 & Figure 1).

On the other hand, 211 (70.3%) of the total participants were non-smokers, 89 (29.7%) were smokers, and 111 males (55.5%) were non-smokers, and 89 males (44.5%) were smokers, whereas all females were non-smokers. There no statistically significant differences in the present study between Arabs, Asians, and African participants in gender and smoking. Regarding number of cigarettes/day

Table 1. Age of participants.

	Age		ANOVA	
	Range	**Mean ± SD**	**F**	**P-value**
Group I (AR)	14-89	32.3203 ± 14.543		
Group II (AS)	21-76	42.9603 ± 12.703	16.253	<0.001*
Group III (AF)	18-81	39.3203 ± 12.9193		
Tukey's test				
(I) AR & (II) AS		(I) AR & (III) AF	(II) AS & (III) AF	
<0.001*		**<0.001***	**0.135**	

AR: Arabs. AS: Asians. AF: Africans. I: Group I, II: Group II. III: Group III.

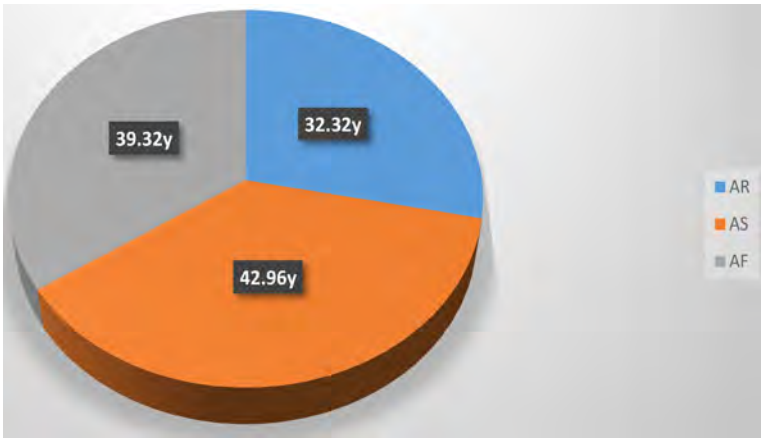


Figure 1. The mean of age of the study groups. AR: Arabs. AS: Asians. AF: Africans.

(NCs/D), there was an increase in the mean of NCs/D more than ten cigarettes per day (>10 Cs/D) without statistical significance differences in group I, II & III (14.13 ± 6.9), (12.13 ± 4.3) and (11.9 ± 5.5). Moreover, of the 300 participants, 271 (90.3%) had HbA1c <7% and 29 (9.7%) had HbA1c >7%. Consequently, the number of patients in the current study with HbA1c <7% is more than HbA1c >7% in group I, II & III without statistical significance differences (p > 0.05) (Table 2 & Figure 2).

Tables 3-5 and Figures 3-5 show the gingival and oral hygiene status, Periodontal parameters of periodontitis (severity) staging, and complexity of participants within racial/ethnic groups (group I, II, and III) in the current study.

Table 2. Characteristics of participants.

		Groups						Chi-square	
		AR		AS		AF		X^2	P-value
Age	Range	14 - 89		21 - 76		18 - 81		16.253	<0.001*
	Mean ± SD	32.32 ± 14.54		42.96 ± 12.70		39.32 ± 12.92			
Gender	Female	34	34.0%	33	33.0%	33	33.0%	0.030	0.985
	Male	66	66.0%	67	67.0%	67	67.0%		
Smoking	<10 Cs/D	70	70.0%	69	69.0%	72	72.0%	0.224	0.894
	>10 Cs/D	30	30.0%	31	31.0%	28	28.0%		
Diabetic	HbA1c >7%	5	5.0%	11	11.0%	13	13.0%	4.334	0.114
	HbA1c <7%	95	95.0%	89	89.0%	87	87.0%		

±SD: Standard deviation. Cs/D: Cigarettes/day. HbAc1: Glycosylated hemoglobin.

Table 3. Gingival and oral hygiene status of participants.

		Groups						Chi-square	
		Group I (AR)		Group II (AS)		Group III (AF)		X^2	P-value
		N	%	N	%	N	%		
GBI	<10	14	14.0%	11	11.0%	11	11.0%	0.788	0.940
	10 - 30.	29	29.0%	32	32.0%	29	29.0%		
	>30	57	57.0%	57	57.0%	60	60.0%		
ANOVA test									
PCR %		Mean ± SD		Mean ± SD		Mean ± SD		F	P-value
		54.83 ± 27.01		59.88 ± 22.51		51.77 ± 27.12		2.554	0.079
Tukey's test									
		I&II			I&III			II&III	
		0.346			0.675			0.067	

GBI: Gingival bleeding index. N: Number. PCR: Plaque control record.

Table 4. Periodontal parameters of periodontitis (severity) staging.

		ANOVA			Tukey's test		
		Mean ± SD	F	P-value	I & II	I & III	II & III
CAL	AR	4.760 ± 1.980	6.798	<0.001*	0.002*	0.013*	0.817
	AS	5.785 ± 2.029					
	AF	5.605 ± 2.276					
RBL	AR	20.117 ± 10.880	6.911	<0.001*	0.001*	0.258	0.086
	AS	26.850 ± 14.350					
	AF	22.979 ± 13.091					
NMTP	AR	0.210 ± 0.701	4.461	0.012*	0.011*	0.094	0.701
	AS	0.750 ± 1.546					
	AF	0.600 ± 1.531					

CAL: Clinical attachment loss. RBL: Radiographic bone loss. NMTP: Number of teeth missing due periodontal diseases.

Table 5. Periodontal parameters of periodontitis staging (complexity).

		Group						Chi-square	
		AR		AS		AF		X^2	P-value
		N	%	N	%	N	%		
TM	NO	77	77.0%	66	66.0%	78	78.0%	13.812	0.032*
	G I	12	12.0%	13	13.0%	3	3.0%		
	G II	9	9.0%	15	15.0%	12	12.0%		
	G III	2	2.0%	6	6.0%	7	7.0%		
FI	NO	69	69.0%	60	60.0%	60	60.0%	6.084	0.638
	G I	15	15.0%	17	17.0%	18	18.0%		
	G II	11	11.0%	13	13.0%	18	18.0%		
	G III	4	4.0%	8	8.0%	3	3.0%		
	G IV	1	1.0%	2	2.0%	1	1.0%		
TFO	NE	94	94.0%	90	90.0%	96	96.0%	2.959	0.228
	PO	6	6.0%	10	10.0%	4	4.0%		
BC	NO	78	78.0%	77	77.0%	78	78.0%	0.038	0.981
	PO	22	22.0%	23	23.0%	22	22.0%		
L20RT	NO	98	98.0%	83	83.0%	94	94.0%	15.923	<0.001*
	PO	2	2.0%	17	17.0%	6	6.0%		
ANOVA test									
						F		P value	
PPD	AR	3.660 ± 0.913				5.713		0.004*	
	AS	4.175 ± 1.173							
	AF	3.910 ± 1.129							
Chi-square									
		AR		AS		AF		X^2	P-value
		N	%	N	%	N	%		
(PBL)	Absent	35	35%	17	17.0%	30	30.0%	18.265	0.006*
	H	49	49%	66	66.0%	52	52.0%		
	V	7	7%	2	2.0%	1	1.0%		
	H + V	9	9%	15	15.0%	17	17.0%		

TM: Tooth mobility. FI: Grade of function involvement. TFO: Secondary trauma from occlusion. BC: Bite collapse. L20RT: Less than 20 remaining teeth. PPD: Periodontal pocket depth. PBL: Pattern of bone loss. NO: No present, G: Grade. NE: Negative, PO: Positive. H: Horizontal. V: Vertical.

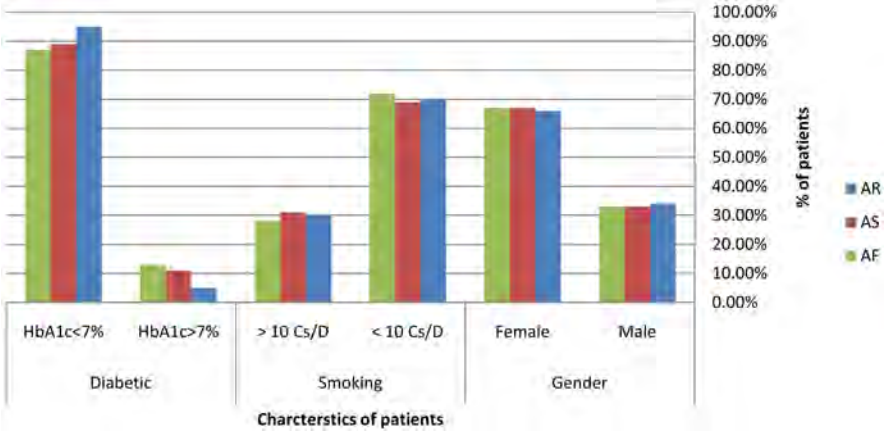
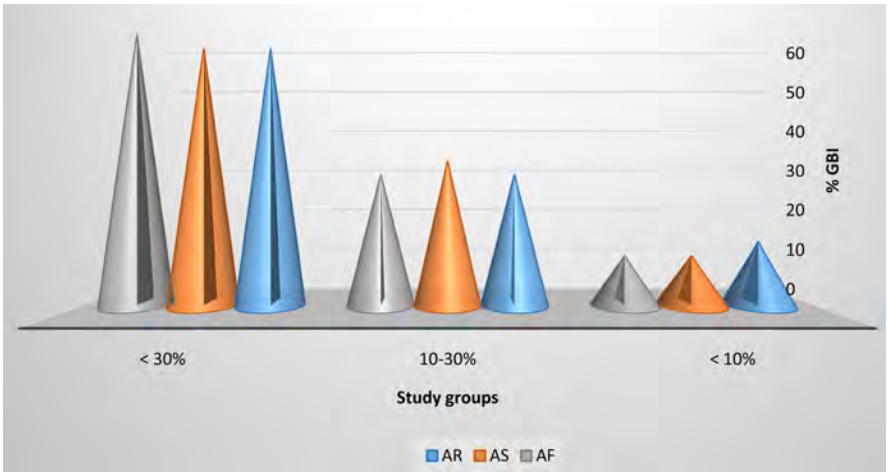
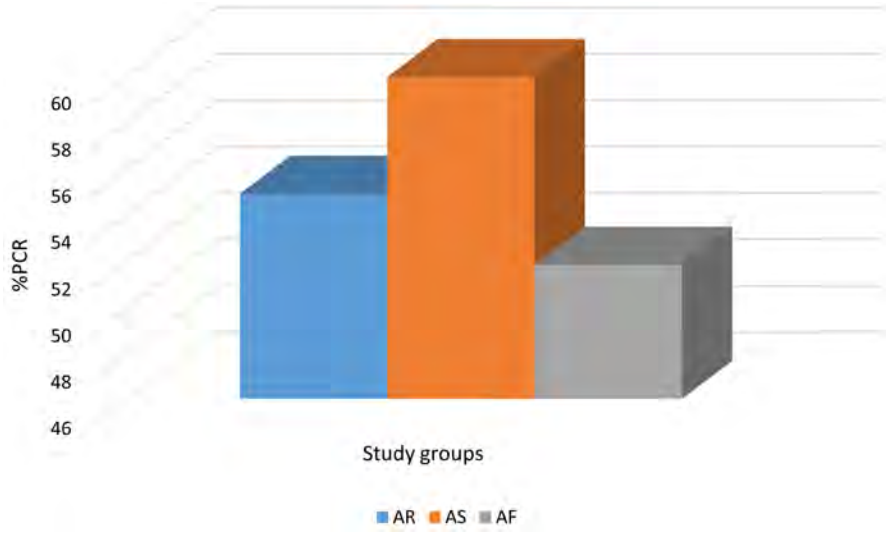


Figure 2. Characterstics of participants. Cs/D: Cigarettes/day. HbAc1: Glycosylated hemoglobin. AR: Arabs. AS: Asians. AF: Africans.

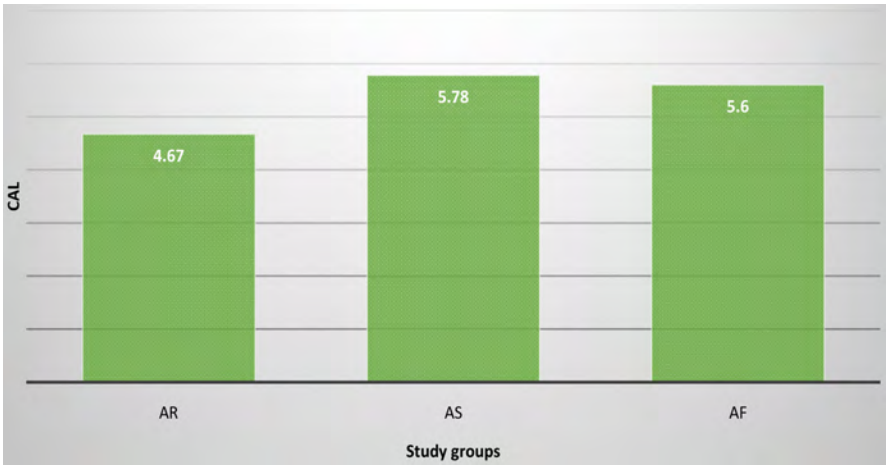


(a)

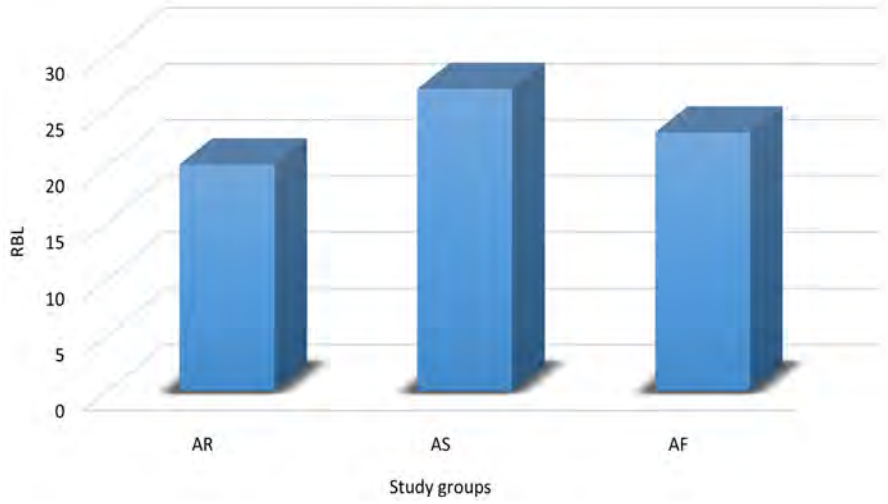


(b)

Figure 3. (a): Gingival bleeding index. % GBI: Percentage of gingival bleeding index. AR: Arabs. AS: Asians. AF: Africans. (b) The percentage of plaque control record. % PCR: Percentage of plaque control. AR: Arabs. AS: Asians. AF: Africans.



(a)



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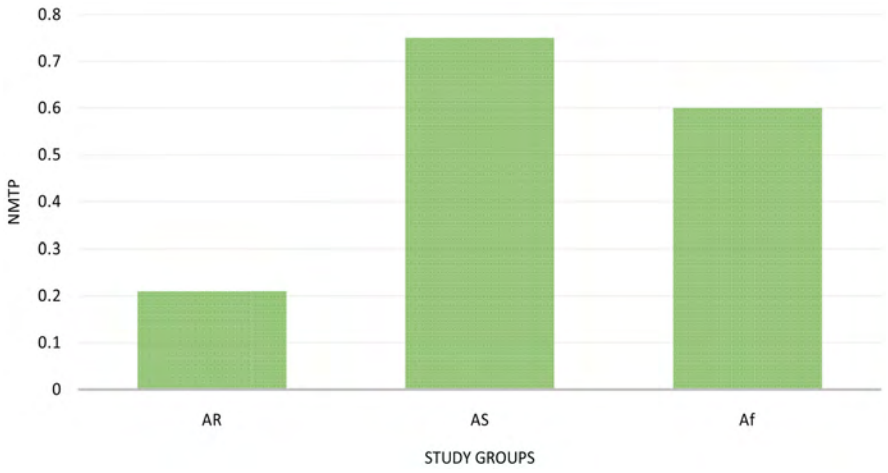

(c)

Figure 4. (a): Clinical parameters of periodontitis staging (CAL). CAL: Clinical attachment loss. AR: Arabs. AS: Asians, AF: Africans. (b) Clinical parameters of periodontitis staging (RBL). RBL: Radiographic bone loss, AR; Arabs, AS: Asians, AF: Africans. (c) Clinical parameters of periodontitis staging (NMTP). NMTP: Number of missing teeth due to periodontitis. AR: Arabs. AS: Asians, AF: Africans.

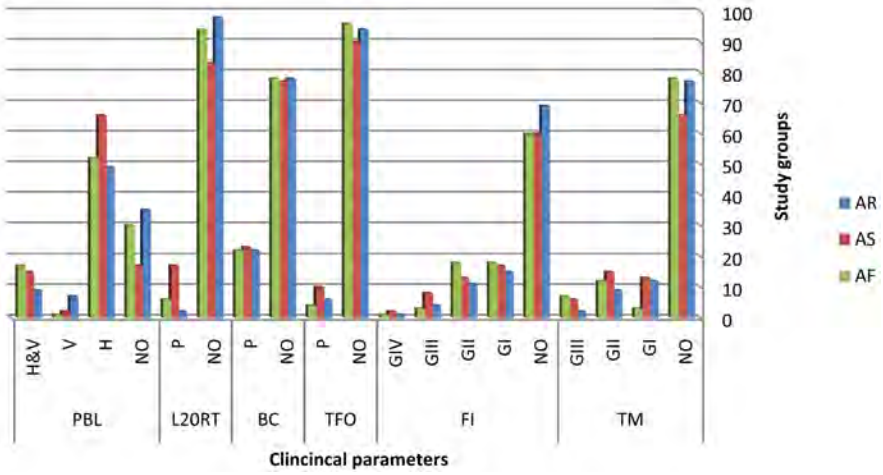

Figure 5. Clinical parameters of periodontitis staging complexity. TM: Tooth mobility. FI: Grade of function involvement. TFO: Secondary trauma from occlusion. BC: Bite collapse. L20RT: Less than 20 remaining teeth. PPD: Periodontal pocket depth. PBL: Pattern of bone loss. NO: No present, G: Grade. NE: Negative, PO: Positive. H: Horizontal. V: Vertical.

There was an increase in PCR, GBI, CAL, RBL, NMTP, and PPD among the patients of Asians more than group Arabs and Africans without statistical significance differences of PCR and GBI in the comparison between these three groups according to ANOVA test, Tukey's test, and Chi-square test. There were highly statistically significant differences between these groups according to the ANOVA test in CLA, RBL, NMTP, and PPD. On the other hand, there were differences in periodontal parameters of periodontitis severity without statistical significance differences according to Tukey's test except between Arabs and Africans in CAL, where there were statistical significance differences ($p = 0.013$).

There was no TM, FI, TFO, BC, and L 20 RT detected among most of the patients of groups, and there was a statistically significant difference in TM and highly statistically significant difference in L20 RT without statistically significant differences in FI, TFO, and BC in the comparison between Arabs, Asians, and Africans. Regarding the pattern of bone loss, horizontal bone loss was more than vertical, and both horizontal & vertical with highly statistically significant differences ($p = 0.006$). It was in Africans more than Arabs and Asians. Moreover, the Vertical bone loss of Arabs was more than Asians and Africans, while both horizontal and vertical bone loss of Africans was more than Arabs and Asians. There was a correlation between the plaque control record (O'Leary index) and the clinical parameters of periodontitis severity and progression except for furcation involvement (Table 6).

Table 7 and Figure 6 show gingivitis extent, severity, and grading where the localized gingivitis among the participants of groups I, II, and III was 43%, 43%, and 40%, and the generalized gingivitis was 57%, 57%, and 60% respectively. There were no significant differences in the extent of gingivitis between Arabs and Asians, but it was more among Africans compared to Arabs and Asians.

Table 6. Correlation between PCR, age, and periodontitis staging and grading.

Correlations		PCR	
		r	P-value
Age		0.134	0.02*
Periodontitis (severity) staging	CAL	0.330	<0.001*
	RBL	0.221	<0.001*
	NMTP	0.180	0.002*
Periodontitis Staging complexity	PPD	0.313	<0.001*
	TM	0.233	<0.001*
	FI	0.104	0.073
Periodontitis Progression (grading)	No. Cs/D	0.321	0.002*
	% HbA1c	0.451	0.0311*

CAL: Clinical Attachment loss. RBL: Radiographic bone loss, NMTP: Number of missing teeth due to periodontitits, PPD: Periodontal pocket depth. TM: Tooth mobility. FI: Furcation involvement. No. Cs/D: Number of cigarettes per day. % HbA1c: Percentage of Glycosylated hemoglobin.

Table 7. Gingivitis extent, severity and grading.

Clinical Findings		Group I	Group II	Group III
Extent	Localized	43%	43%	40%
	generalized	57%	57%	60%
Severity	Mild	14%	11%	11%
	Moderate	29%	32%	29%
	Severe	57%	57%	60%
Grade	1	14%	13%	12%
	2	14%	17%	18%
	3	14%	17%	19%
	4	30%	27%	26%
	5	28%	26%	25%

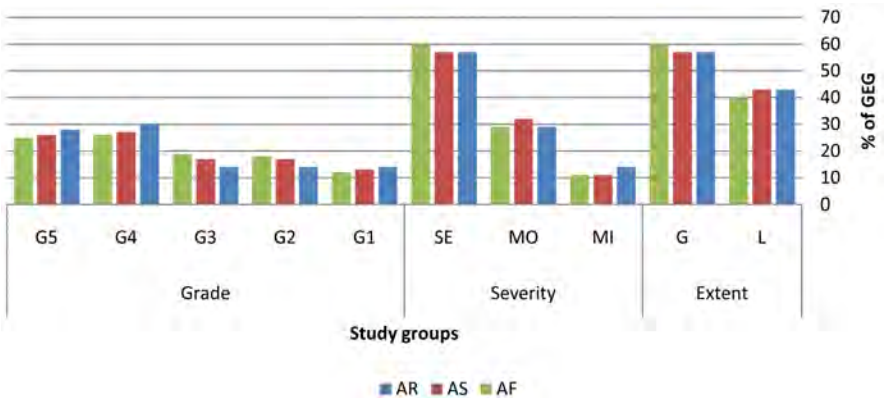

Figure 6. Gingivitis extent, severity and grading. L: Localized. G: Generalized. MI: Mild. MO: Moderate. SE: Severe. G1: Grade 1. G2: Grade 2. G3: Grade 3. G4: Grade 4. G5: Grade 5.

Mild gingivitis among Arabs was more, while moderate and severe gingivitis among Asians was more. More, detailed grading of gingivitis is also in Table 7 and Figure 7. Grade 1, 4, and 5 gingivitis of Arabs more than Asians and Africans, and Grade 2 and 3 gingivitis of Africans more than Arabs and Asians.

Table 8 and Figure 7 exhibit the clinical parameters of periodontitis extent and severity within each group. In all groups, generalized periodontitis was higher than localized periodontitis. Arabs displayed the highest periodontitis severity where 18% of them reached stage IV of periodontitis (very severe), followed by African and Asian 17% and 16% reached stage IV periodontitis. The progression of periodontitis rate of the participants in the current study increased for all groups. Table 9 and Figure 8 displayed that the majority (64%, 61% & 68%) of Arabs, Asians, and Africans had a moderate rate of periodontitis, while 17%, 21%, and 20% of them had a rapid rate of periodontitis compared to 19%, 18%, and 12% had a slow rate of periodontitis.

4. Discussion

Periodontitis comprises one of the global problems in the oral cavity [1]. The main objective of the evaluation studies for severity and progression of periodontitis is to supply the dental practitioners and periodontists with significant data to help them in the diagnosis and the assessment of prognostic factors with

Table 8. Periodontitis extent and severity (stages).

Groups	Extent		Severity (CAL, RBL, NMTP, PPD, FI)				Complexity (IV) (TM, TFO, BC, <20 RT)
	L	G	I	II	III	IV	
AR	86%	14%	33%	13%	36%	00%	18%
AS	89%	11%	34%	10%	40%	3%	13%
AF	86%	14%	35%	10%	38%	3%	14%

AR: Arabs. AS: Asians. AF: Africans. L: Localized. G: Generalized. I: Stage I. II: stage II, III: Stage III and IV: Stage IV. CAL: Clinical Attachment loss. RBL: Radiographic bone loss, NMTP: Number of missing teeth due to periodontitis, PPD: Periodontal pocket depth, TM: Tooth mobility. FI: Furcation involvement. TFO: Secondary trauma from occlusion, BC: Bite collapse, <20 RT: <20 remaining teeth.

Table 9. Periodontitis progression (grading).

		A (% bone loss/age <0.25) and (Non-smokers and non-diabetic)	B (% bone loss/age 0.25 to 1.0) and (<10 Cs/D or HbA1c <7.0%)	C (% bone loss/age >1.0) and (>10 Cs/D or HbA1c ≥7.0%)
Grade modifiers	AR	19%	64%	17%
	AS	18%	61%	21%
	AF	12%	68%	20%

A: Grade A. B: Grade B. C: Grade C. AR: Arabs. AS Asians. AF: Africans. No. Cs/D: Number of cigarettes per day. % HbA1c: Percentage of Glycosylated hemoglobin.

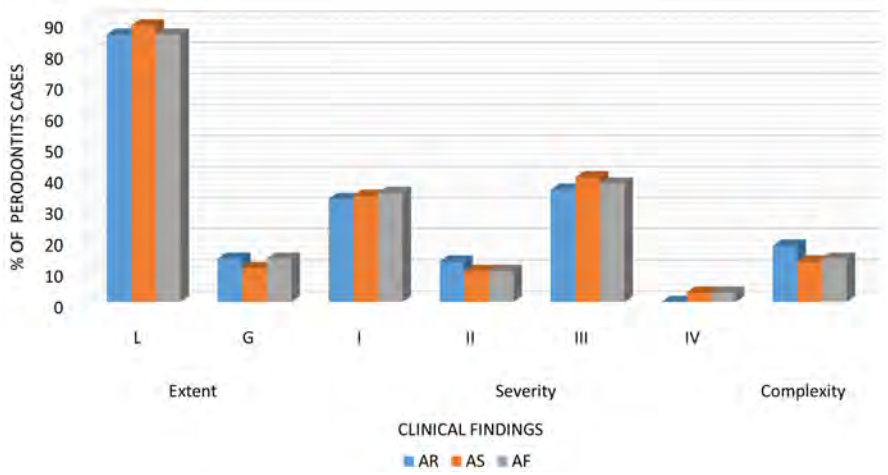

Figure 7. Periodontitis extent and severity (staging). L: Localized, G: Generalized. I: Stage I. II: stage II, III: Stage III and IV: Stage IV. AR: Arabs. AS: Asians. AF: Africans.

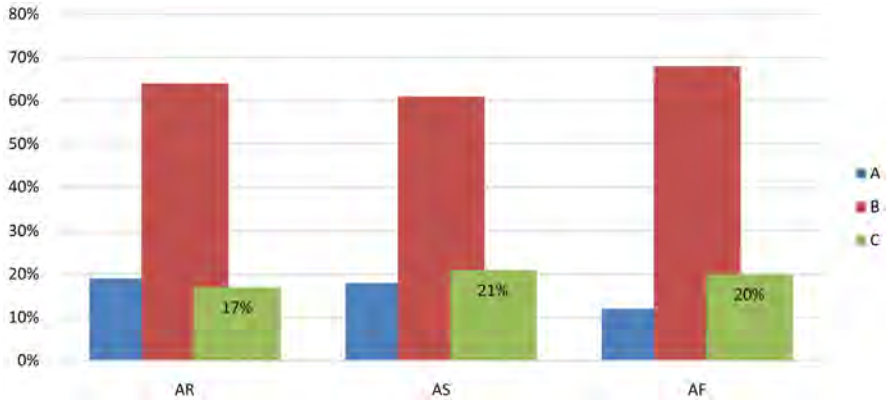

Figure 8. Periodontitis progression (grading). A: Grade A. B: Grade B. C: Grade C. AR: Arabs. AS: Asians. AF: Africans.

planning periodontal therapy. These data comprise the presence of plaque, gingival bleeding, clinical attachment loss, radiographic bone loss, and periodontal pocket formation [32]. Moreover, age, smoking, and other factors associated with socioeconomic status like expatriation [33] [34] [35].

Based on our information, the present study is the first study conducted on selected expatriate population-based samples living in the same area and the same environmental conditions to assess the severity and progression of periodontitis among multi-ethnic patients in Aseer region, Saudi Arabia. This study detected differences in severity and progression of periodontitis among the three ethnic groups, and there were correlations between oral hygiene status and age. Moreover severity, and progression of periodontitis. These findings consistent with many previous studies that have exhibited periodontitis more severe in some ethnic groups [36] [37], and other studies displayed that progression of periodontitis was varying among ethnic groups [35] [38].

The results displayed that 57% of Arabs, 57% of Asians, and 60% of Africans had gingival bleeding more than 30% and that means generalized severe gingivi-

tis in 2017 classification compared to 43% of Arabs, 43% of Asians, and 60% of Africans had localized mild and moderate gingivitis that means gingival bleeding was less than 30%. Regarding grading of gingivitis grade 4, it is more than other grades, but the grading of gingivitis among Arabs is more than Asians and Africans. The present study revealed that most of the participants were suffering from gingivitis with periodontitis. This finding is similar to the study results of Idrees, *et al.* [39]. Moreover, Zhang, *et al.* detected that gingival inflammation affected 97.9% of Chinese adults and 95.7% of American adults [40]. It is well known that there is a closed association between dental plaque and gingivitis, and this demonstrates the association in this study between plaque formation and gingivitis among all participants [41].

In 2017, periodontitis was assessed based on the attachment loss in the interdental area (CAL) at ≥2 mm or as buccal CAL ≥3 mm with >3 mm pocket formation on ≥2 mm teeth [42].

The main objective of the clinical examination was to clarify whether the occurrence and measure of attachment loss varied among the three ethnic groups. The attachment loss was significantly different among the three ethnic groups, but there was an increase in attachment loss in Asians more than Arabs and Africans. The clinical periodontal parameters reflected the severity of periodontitis among the participants in the current study.

In periodontics, radiographic examination supplements the clinical examination, helping to diagnose periodontitis [43]. Several previous studies revealed that the prevalence of horizontal bone loss more than vertical bone loss among the patients of periodontitis. These findings are similar to those found by this study which appeared that the horizontal bone loss among Arabs, Asians, and Africans participants more than vertical bone loss [44] [45] [46].

There was an association between an increase in age and clinical attachment loss. These findings are comparable with Neely *et al.*, who clarified a positive correlation between age and clinical attachment loss [33].

When compared with the previous Libyan study, there were a high percentage of participants who had shallow pockets and deep pockets whereas this study exhibited that most Arabs participants had shallow pockets [47].

In the present study, there was an association between an increased HbA1c level of more than 7% and Clinical attachment loss, the gingival bleeding index where the African participants had HbA1c level of more than 7% moreover clinical attachment loss, gingival bleeding index more than Arabs and Asians participants. These results are consistent with previous studies that revealed that there was a positive correlation between an increase of HbA1c level and clinical attachment loss, gingival bleeding index [48] [49]. Surprisingly, Africans had a higher value of glycosylated hemoglobin than Arabs and Asians, with fewer smokers than the overall study participation. These results indicate that the destruction of periodontal tissues more among Africans than Arabs and Asians, Consequently Africans may have other risk factors linked to this racial/ethnic

group, which need more study.

The current study assessed the association of the presence grade of tooth mobility and other results such as radiographic bone loss, tooth loss due to periodontitis, furcation involvement, secondary occlusal trauma, bite collapse and less than 20 remaining teeth with a specific ethnic group where these periodontal parameters were more among Asians participants more than Arabs and Africans participants. These findings are consistent with an increased plaque control record percentage among Asian participants more than Arabs and African participants. In another previous study, there was a correlation between the degree of tooth mobility, the amount of radiographic alveolar bone loss, and periodontal pocket depth. Similarly, there was an increase in tooth mobility, the amount of radiographic alveolar bone loss, and periodontal pocket depth among Asian participants more than Arabs and African participants [50] [51].

Moreover, there was an increase in these clinical parameters among consumers of ≥10 cigarettes/day (Asian participants) more than other ethnic groups in this study. These results agree with the results of earlier studies that exhibited an increase in tooth mobility and severity of periodontal destruction among smokers more than non-smokers [52] [53].

On the other hand, there was no association between the type of radiographic alveolar bone loss (horizontal or angular). and other clinical parameters of periodontal destruction among the ethnic groups of the current study, where the horizontal bone loss was more among Asian participants whereas the angular was more among Arabs, few studies have examined the relationship between the type of radiographic alveolar bone loss and progression of periodontitis [54].

Borrell et al. detected that African-Americans had periodontitis more severity than other populations in the United States [55]. Consistent with the clinical findings of the current study detected that African participants had higher severity and progression periodontitis than Arabs and Asians. The results of this study exhibited that most Africans and Arabs participants had generalized periodontitis stage III and IV, grade B more than Asians, whereas most Arabs and Asians had localized periodontitis stage I and II, grade A among most Arabs and grade C among most of Asians more than Africans due to most of Asians were heavy cigarette smokers (more than 10cigarettes per day). Furthermore, there was an association between the increase of the progression of periodontitis and an increase of cigarettes smoked per day among the subjects in the current study where the mean age of Asian participants who were with grade (C) periodontitis more than the mean age of Arabs and Africans participants who were with grade (A) and (B) of periodontitis respectively. These clinical findings were in agreement with former studies, which indicated an increase in periodontitis with an increase in age [56] [57]. These clinical findings also corresponding with other clinical and epidemiological studies that exhibited that periodontal disease increases with the greater the number of cigarettes smoked a day [58].

In other previous studies on different ethnic groups, Africans had a higher

severity and progression of periodontitis than other groups [59]. Similarly, in this study, the severity of periodontitis among Africans and Asians is more than Arabs but the complexity of periodontitis severity among Arabs is more than Asians and Africans.

5. Strength and Limitations

The strength and limitation of the present study depend on the racial/ethnic variations of its participants. Moreover, there is very little knowledge about the severity of periodontal diseases of expatriates in Saudi Arabia, compares to each other in this country. This study did not collect any information from participants about the education level, socioeconomic status, oral hygiene measures, and the dental clinics' visit frequency. As there are different origins of expatriates in Saudi Arabia, it is essential that we fully understand the risk factors of periodontal disease among the racial/ethnic groups of the current study to help them and reduce the severity and progression of periodontitis. Additional studies with larger sample sizes are necessary to explain the impact of racial differences on oral health and periodontal disease extent, staging and grading.

6. Conclusion

In conclusion, the present study has reported changes in the severity and progression of periodontal diseases among the three ethnic groups, but the variables that may be associated with ethnicity did not examine such as, education level, economic level, and occupational status. Therefore, the results of this study suggest that these variables may affect the severity and progression of periodontal diseases.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Saudi Consensus for Low-Premixed Insulin Analogues in Type 2 Diabetes: Consensus Report

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Abstract

We learned from the literature that premixed insulins are short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin in a fixed ratio, addressing FBG and PPBG in one injection. There are two categories; high-mix and low-mix premixed insulins. We, a Saudi task force, gathered to develop an explicit, evidence-based consensus for the use of the low-mix premixed insulin for better glycemic control. The treatment with premixed aspart 30 was non-inferior to treatment with premixed insulin lispro 25. In addition, Self-monitored blood glucose levels were comparable. Safety profiles were similar between both treatments, as was the incidence of hypoglycemic episodes. The switch between both products of the low-mix family can be carried out without any problem. Both products of the low-mix premixed insulin analogues aspart 30/70 and premixed insulin lispro 25/75 have comparable efficacy and safety as shown from the medical literature. Therefore, we can change from one to another safely as demonstrated by the US FDA statement. In addition, the ergonomic features of KwikPen's design and function may offer important advantages for the user during insulin administration.

Keywords

Low-Mix, Premixed Insulin, Lispro 25/75, Aspart 30/70

1. Introduction

According to the International Diabetes Federation (IDF) Diabetes Atlas, the worldwide prevalence of diabetes mellitus (DM) is expected to become 9.9% by the year 2045 with a total number of 629 Million [1]. It is associated with significant morbidity and mortality across the globe. Its prevalence is rising rapidly in Saudi Arabia [2]. To address both the fasting blood glucose (FBG) and post-prandial blood glucose (PPBG), the premix insulin formulations provide a combination of both rapid/short-acting and intermediate/long-acting insulins in a fixed ratio, in a single injection. There are two categories; high-mix and low-mix premixed insulins. We, a Saudi task force, gathered to develop an explicit, evidence-based consensus for the use of the low-mix premixed insulin for better glycemic control. This article has the recommendations of this expert panel.

1.1. Premixed Insulins

Premixed insulins are short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin in a fixed ratio, addressing FBG and PPBG in one injection. They are listed hereunder in **Table 1**.

They have some advantages over the self-mixed insulin. These advantages include accurate dosage, efficacy, and patient convenience. All can be translated into increased compliance and better long-term control of DM [3] [4].

1.2. Pharmacokinetics of Insulin Analogues

The pharmacokinetics of medication includes several parameters: the absorption, the distribution, the metabolism, and the elimination. Insulin absorption is

Table 1. Premixed insulins.

Insulin Type	Trade Name	Onset of Action	Duration of Action
Premixed			
Human regular/NPH	Human Mixtard 30/70	Variable	Variable
Premixed analogues			
High-mix			
Lispro/lispro protamine	Humalog Mix 50/50	Variable	Variable
Aspart/aspart protamine	NovoMix 50/50	Variable	Variable
Low-mix			
Lispro/lispro protamine	Humalog Mix 25/75	Variable	Variable
Aspart/aspart protamine	NovoMix 30/70	Variable	Variable

derived principally by measuring the concentration of circulating insulin over time from the start of subcutaneous injection. That can be evaluated by the euglycemic clamp technique in both normal subjects and diabetic patients (type 1 and 2 diabetes). The measures can provide a comprehensive description of the way in which the body processes the insulin from administration to elimination. Typically, the concentrations of insulin should increase or decrease by an increase or decrease in the administered dose. In addition, insulin concentration curve over time should coincide with the wanted glycemic lowering profile. Therefore, for the rapid-acting insulin analogues, the concentration of insulin should peak very quickly after the injection and be rapidly metabolized, and eliminated. The currently available rapid-acting insulins have duration of action of 3 - 5 hours according to the injected dose. Meanwhile, the concentration of the long-acting insulin analogues needs to be stable and uniform. In addition, it should be noted that current basal insulin analogues have a waning insulin concentration that may not accommodate for the morning increase in the need for insulin to cover what is called the dawn phenomenon; the transitory increase in insulin resistance in the morning [5] [6] [7].

As for the premixed insulin analogues (biphasic), the perfect profile is the combination of both a rapid-onset and peak insulin action following the injection. That is to cover the postprandial needs, followed by a rapid return to a long plateau to cover the basal needs. Current formulations of premixed biphasic insulins are not ideal in this respect (**Figure 1**) [5] [8] [9].

The rapid-acting insulin analogues' profiles simulate the normal physiological insulin secretion in response to meals better than the regular human insulin, with a faster onset and higher maximal concentration. However, the profiles of long-acting insulin analogues are not wholly flat and do not remain steady over the day. Premixed insulin analogues show more rapid absorption relative to premixed human insulin and have different peak concentrations in relation to the dose of the soluble rapid-acting component. The return to basal insulin levels is slow and uneven. This part of the biphasic insulin profile is known as the

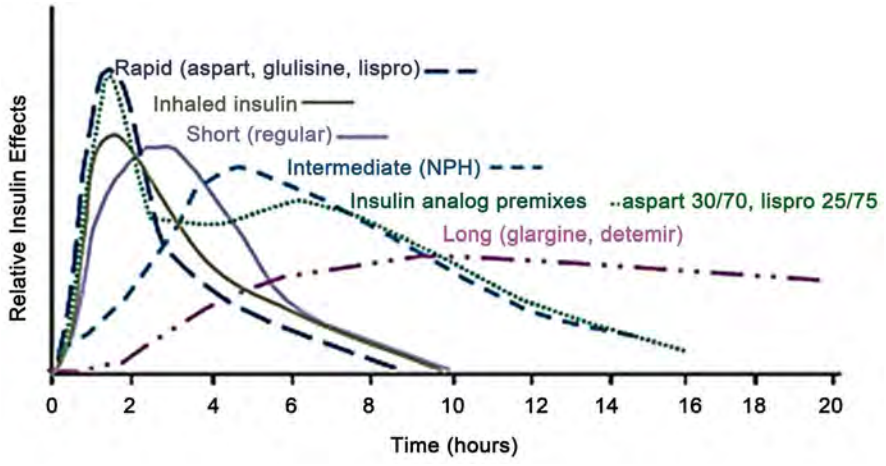

Figure 1. Representative rime action profiles of selected insulins [8] [9].

shoulder, which occurs due to the interaction between soluble and protaminated insulin molecules [10] [11] [12] [13] [14].

1.3. Pharmacodynamics

The pharmacodynamic insulin profile is alike to the pharmacokinetic profile in shape. For the rapid-acting insulin analogues, it is a rapid onset and offset, and for long-acting insulin analogues, it is a long, flat, and constant profile. In a clamp study, the blood glucose levels of the subjects are kept within a certain range by infusing IV glucose. The amount of infused glucose to maintain the blood levels depicts the amount of its uptake into the cells due to activation of insulin receptors. This is called the glucose infusion rate (GIR) [5] [15].

The kinetics and dynamics of rapid-acting insulin analogues (aspart and lispro) are similar, as shown in **Figure 2** [16].

Glucose lowering effect from published pharmacodynamics studies conducted in patients with T2DM as measured by the glucose infusion rate (GIR) for insulin aspart (0.3 U/kg) [17], human soluble insulin (0.3 U/kg) [17], biphasic insulin aspart 30/70 (0.6 U/kg) [11], biphasic human insulin 30 (0.6 U/kg) [11], insulin detemir (0.8 U/kg) [10] and insulin glargine (0.8 U/kg) [10]. All insulin preparations were administered at time = 0 h. In those patients, both insulin aspart and insulin lispro given just before meals, have reduced the rise of the 2-h PPBG by an 18% - 48% reduction compared to human insulin given 30-min before meal time [12] [18] [19] [20].

Cross-over trials showed that the pharmacodynamics of insulin lispro mix 25 [21] [22] have a lower peak rise in BG compared with premixed human insulin and NPH. In addition, premixed insulin aspart 30 had 44 and 34% lower PPBG concentrations compared with premixed human insulin 30 after breakfast and dinner, respectively [23]. In addition, these results are consistent with the differences between rapid-acting insulin analogues and human insulin [5].

Moreover, for those requiring higher doses of rapid-acting insulin, there is good evidence showing the relative increases in early PPBG utilization with the high-mix insulin analogues (e.g., premixed insulin aspart 50/50 and 70/30, and

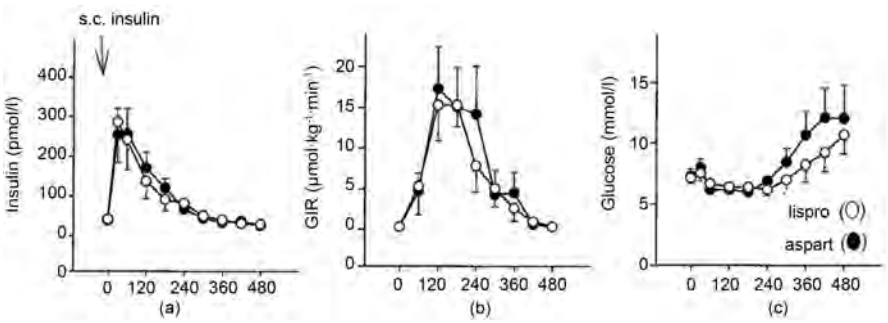

Figure 2. Insulin aspart and insulin lispro: (a): Serum insulin levels before and after subcutaneous injection (at 0 min) of insulin aspart or insulin lispro. (b): GIR is needed to prevent hypoglycemia in the same patients. (c): Plasma glucose concentrations before and after subcutaneous injection of insulin aspart or insulin lispro in the same patients [16].

premixed insulin lispro 50/50 and 75/25) [24] [25] [26].

Insulin analogues provide physicians the ability to more closely mimic the normal physiology of insulin and to select different regimens depending on patient preferences and lifestyle. Faster onset of action of rapid-acting insulin analogues has improved postprandial glycemic control in patients with T2DM; and more predictable glycemic lowering profiles of the insulin analogues have also led to reductions in reported nocturnal hypoglycemia, particularly comparing long-acting insulin analogues with NPH [5] [12] [13] [23] [27] [28] [29] [30].

Finally, whilst premixed insulin analogues have been shown to be associated with a lower incidence of nocturnal hypoglycemia compared with premixed human insulin and help in the intensification of insulin therapy, the protaminated/precipitated component does not provide the same duration of action or profile of physiological basal insulin replacement. In essence, premixed insulin is a mixture of rapid and intermediate-acting insulin, that is, carrying the same limitations as the individual components. Unfortunately, neither insulin glargine nor insulin detemir is suitable for mixing with other insulin analogues as this mixing substantially alters their pharmacokinetic properties.

In summary, premixed insulin analogues do not have two distinct peaks. Once absorbed, the time of action corresponds to the rapid onset of action of the rapid-acting component, and the duration of action corresponds to the intermediate insulin component. The peak of action of the premixed insulin analogues is unimodal (one distinct peak), corresponding to the maximum effect of the rapid-acting component, and it is steep with a gradual decline. The rapid absorption is because of the rapid-acting component and this rapid pronounced onset of action signifies that these analogues can be utilized immediately before or following a meal [11] [25] [31] [32] [33].

1.4. Clinical Utility

It is not clear who could most benefit from the utilization of the premixed insulin analogues. However, based on data from one meta-analysis (Giugliano *et al*., 2011) [34] and the DURABLE study [35], it can be concluded that that certain people with DM could benefit more by starting an insulin treatment with this type of therapy. Those categories of patients who have HbA1c around 8.5% have higher elevations in PPBG are less willing to carry out several SMBG measurements throughout the day [35]. Whereas the low-mix 25 could be suitable for those patients who have not reached adequate PPBG levels [36] [37] [38], the high-mix 50/50 can enhance the premixed insulin therapy and is good for those who are already using premixed analogues [39].

The premixed insulin analogues 50/50 can also be an option for those using the basal insulin in addition to multiple doses of rapid-acting insulin but are not compliant with the regimen of therapy [40] [41]. In addition, these higher premixed insulins could be an initial choice of therapy for those needing higher daily doses of rapid-acting insulins or those who eat a high carbohydrate meal. [39] [42] [43].

It is well established that people with T2DM who do not achieve glycemic targets despite the lifestyle modifications, and use of one or more oral antidiabetic drugs (OADs) should start insulin therapy [44] [45]. The type of insulin used in the initial phase depends on the insulin resistance degree and the quantity of consumed food at each meal [33] [46] [47]. Moreover, recent evidence suggests that the low-mix premixed insulin analogues 25 provides a similar glycemic control to that of insulin glargine plus lispro in insulin-naïve people with uncontrolled DM on OADs. Non-inferiority of the low-mix regimen 25 was shown in such category of patients [48].

Once the doctors have opted for one of the low-mix premixed insulin analogues, either the aspart 30/70 or lispro 25/75, insulin can be given at the start at a dose of 0.1 U/kg before breakfast. Then, the dose can be titrated or repeated before dinner on the following days, depending on individual needs [5]. This titration is based on the BG levels pre-meals. Insulin is to be adjusted every three days, according to the average BG levels at the respective times [49]. If HbA1c is not at targets at four months after the initiation of insulin despite an appropriate BG levels before meals, then PPBG should be evaluated [25]. For those patients already on the basal insulin therapy who may not achieve the HbA1c targets due to high PPBG levels despite good fasting levels, the premixed insulin analogues can be used. The total dose of the premixed insulin analogues per day could be given on a 1:1 ration (the same total daily dose). Half the dose is to be given before the breakfast and the other half before the dinner [49].

1.5. Are All the Low-Mix Premixed Insulin Analogues the Same?

In a randomized, multinational, open-label, company sponsored (Novo Nordisk) crossover comparison study of premixed insulin aspart 30 and premixed insulin lispro 25 in adult patients with T2DM, Niskanen *et al*. (2004) compared their efficacy and safety profiles. The premixed insulin aspart 30 (30% soluble insulin aspart and 70% protaminated insulin aspart) and the premixed insulin lispro 25 (25% soluble insulin lispro and 75% neutral protamine lispro were used in a BID injection regimen in patients with T2DM. In addition, they assessed the patients' preference for pen devices. Glycemic control was assessed by measuring the HbA1c after three months of treatment [50].

A total of 151 patients with T2DM were screened. Inclusion required insulin treatment for the past six months, total daily insulin dose <1.80 IU/kg, age more than 18 years, HbA1c <12%, and body mass index <35 kg/m^2. Patients had to be eligible for BID mixed insulin treatment and be able and willing to perform SMBG. Previous therapy with insulin analogues or the use of OADs within the last month was not allowed. Furthermore, those cases with abnormal renal, hepatic, or cardiac functions were excluded. Also, other exclusion criteria included severe uncontrolled hypertension, allergy to the trial medications, pregnancy, or drug or alcohol abuse. Nine patients did not fulfill the inclusion or exclusion criteria, and five decided to withdraw before randomization. Randomization was

carried out using an interactive voice response system. The investigator telephoned the system and obtained the treatment sequence from the underlying randomization codes, thereby ascertaining unbiased treatment allocation in the open-label trial design [50].

2. Efficacy Assessments

Glycemic control was assessed by the measurement of HbA1c after 12 weeks of treatment. In addition, short-term glycemic control was assessed by SMBG measurements. OneTouch® Profile® BG meter (LifeScan, Inc., Milpitas, California) were used. Patients were asked to perform a seven-point BG profile on any day in the week prior to the start and end of treatment periods [50].

3. Safety Assessments

Adverse events (AEs) and hypoglycemic episodes were recorded throughout the trial. The investigator classified the AEs as serious or non-serious and assessed the severity of the events. AEs were considered serious if they resulted in death, a life-threatening experience, inpatient hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect. All AEs not fulfilling the above definition were classified as non-serious. AE severity was assessed as mild, moderate, or severe. Relation to the trial product was assessed by the investigator as probable, possible, unlikely, or impossible to assess. Hypoglycemic episodes were classified as major (requiring third-party assistance), minor (BG reading <2.8 mmol/L with or without symptoms of hypoglycemia), or symptoms of hypoglycemia (not confirmed by BG reading). Vital signs (pulse and blood pressure, sitting) were recorded at the beginning and end of each treatment period. Measurements were taken after patients had been resting in a chair for 5 minutes [50].

4. Preference for Pen Device

Patient satisfaction with the pen devices was assessed using two device-specific questionnaires: 1 for the FlexPen and 1 for the Humalog Pen, differing by the device names only. The questionnaires included 16 questions aimed at assessing features of the pens that were related to ease of use, utility and convenience, and confidence in correct diabetes management. In addition, patients were asked to state whether they had experienced any problems using the pens and if so, they were asked to describe them. Each questionnaire was completed at the end of the treatment period in which the patients had used the particular device. The questionnaires were completed by the patients at the clinic before the clinical consultation. While completing the questionnaires, patients were left alone, but with access to a staff member if questions arose. If uncertain about specific questions, the patient was asked to read the question again and answer in the most appropriate way. The patients placed the questionnaire in an envelope and sealed it. At the end of the second treatment period, patients rated the importance of the

features assessed in the device-specific questionnaires. Furthermore, after having used both pen devices, patients' overall pen preference was evaluated using a comparative questionnaire. The patients were asked which pen they found easiest to use and which they would prefer to continue using [50].

5. Characteristics of the Participants

A total of 137 patients were randomized to treatment. Four of the randomized patients were withdrawn during the run-in treatment with biphasic human insulin 30: 1because of an AE and three for other reasons. The mean (SD) characteristics of the remaining 133 patients (79 men, 54 women) exposed to the premixed insulin aspart 30 (Asp 30) and/or the premixed insulin lispro 25 (Lisp25) were as follows: age, 62.3 (9.2) years; body mass index, 28.1 (3.9) kg/m^2; and HbA1c, 8.5% (1.1). The mean duration of diagnosed T2DM was 12.1 (7.1) years (range, 0.6 - 35.8 years). Concomitant illnesses included symptoms related to late T2DM complications. A total of 129 patients completed the trial; four patients withdrew during the first treatment period (two because of AEs considered to be unlikely related to trial products [one receiving Asp 30 and 1 receiving Lisp25], one owing to ineffective therapy (Lisp25), and 1 for other reasons [Asp 30]) [50].

6. Glycemic Control

A total of 132 patients were exposed to Asp 30 and/or Lisp25 and had evaluable efficacy data, thus fulfilling the criteria of the ITT population. Treatment with Asp 30 was non-inferior to treatment with Lisp25 (Table 2). No carryover effects between treatments were indicated. Overall, a mean reduction in HbA1c of ~0.5% from baseline to the end of the second treatment period was observed. The BG levels at each of the seven-time points of the BG profiles were comparable (Table 2). The BG analyses were made without adjustment for baseline

Table 2. Glycemic control with biphasic insulin aspart 30 (30% soluble insulin aspart and 70% protaminated insulin aspart [Asp30]) and biphasic insulin lispro 25 (25% soluble insulin lispro and 75% neutral protamine lispro [lisp25]) as assessed by HbA1c and BG levels after 12 weeks of BID treatment [50].

	Asp 30, mean	Lisp25, mean	Asp 30 - Lisp25, mean	CI	*P*
HbA1c%	8.15	8.01	0.14	0.008 to 0.275	0.082
BG, mmol					
Breakfast	7.6	7.5	0.2	−0.3 to 0.6	0.422
90 min after breakfast	9.5	9.7	−0.2	−1.0 to 0.5	0.524
Lunch	6.5	6.8	−0.4	−0.9 to 0.2	0.168
90 min after lunch	9.7	9.8	−0.1	−0.7 to 0.5	0.746
Dinner	8.7	8.6	0.1	−0.5 to 0.7	0.824
90 min after dinner	9.6	10.0	−0.4	−1.1 to 0.2	0.186
Bedtime	8.6	8.9	−0.4	−1.1 to 0.3	0.291

values; however, such an adjustment did not significantly alter the results. Before lunch, BG was particularly well controlled with both products (6.5 mmol/L with Asp 30 and 6.8 mmol/L with Lisp25). Mean BG was also within the recommended range at the other time points, except before dinner and at bedtime, when the BG target was slightly exceeded. Mean daily insulin doses increased slightly during the overall 24-week treatment period: from 0.65 U/kg to 0.67 U/kg for patients randomized to the Asp 30/Lisp25 sequence and from 0.67 U/kg to 0.71 U/kg for patients in the Lisp25/Asp 30 sequence [50].

7. Safety

The safety population included all 133 exposed patients. The incidence of AEs was similar for both Asp 30 (83 events) and lisp25 (68 events). Upper respiratory tract infections and influenza-like symptoms were the most frequently reported AEs (reported by >5% of patients). Fourteen AEs were serious (11 for Asp 30 and 3 for lisp25); none were judged to be related to trial products. Most AEs were mild (Asp 30: 61.4%; lisp25: 70.6%) or moderate (Asp 30: 33.7%; lisp25: 26.5%) in severity. There was 1 AE withdrawal: a 71-year-old man who was treated for 79 days with Mix25 was diagnosed with malignant neoplasm considered unlikely to be related to treatment. After withdrawal, the patient suffered an acute myocardial infarction and died. The six AEs considered possibly or probably related to trial products were mild and non-serious (Asp 30: 4 events [headaches (2), injection site bruising, and bruising from a fall during a hypoglycemic episode]; lisp25: 2 events [injection site bruising]). During the two 12-week treatment periods, two major hypoglycemic episodes were reported, one for Asp 30 and 1 for lisp25. Fifty-seven patients receiving Asp 30 had 269 minor or symptoms-only hypoglycemic episodes, and 53 patients receiving lisp25 had 233 episodes. Of these minor and symptoms only episodes, 101 episodes with Asp 30 and 79 episodes with lisp25 occurred during the initial four weeks of treatment. These episodes were not included in the statistical analysis. The rate of minor and symptoms-only episodes during the last eight weeks of treatment was 0.69 episode/mo of exposure for Asp 30 and 0.62 episode/mo of exposure for lisp25. As the estimated Asp 30/lisp25 ratio of episodes did not differ significantly from 1 ($P = 0.292$), the risk was comparable. For vital signs, four patients had systolic blood pressure findings slightly and transiently >180 mm Hg. In conclusion, the safety profiles were considered similar for the two treatments [50].

8. Patients' Preference for Pen Device

The device-specific questionnaires assessed features of the pens related to their ease of use, utility and convenience, and to patients' confidence in the correct management of their diabetes (e.g., confidence in setting, controlling, and injecting the correct dose). Analyses of the questionnaire results were performed on the safety population; however, owing to incomplete answers, the exact

number of patients in each crossover analysis was lower (between 111 and 118). Patients were consistently more satisfied with the FlexPen than with the Humalog Pen, with statistically significantly higher scores given to the FlexPen for all 16-device features assessed in the device-specific questionnaires (**Table 3**; all $P < 0.005$). For example, of the 118 patients having answered question 1 in both questionnaires, 63 (53.4%) gave the FlexPen favorably higher scores than the Humalog Pen, whereas 3 (2.5%) patients rated the Humalog Pen higher than the FlexPen. The remaining 52 (44.1%) patients gave equal scores to the two devices [50].

Table 3. Comparison of patients' assessments of the NovoMix® 30 FlexPen®* (FlexPen) and the Humalog® Mix25™† Pen (Humalog Pen) using the device-specific questionnaires [50].

	No. (%) of observations in favor of			
	No. of Paired Observations	FlexPen	Humalog Pen	P
1) How easy/difficult is to read the dose scale?	118	63 (53.4)	3 (2.5)	<0.001
2) How difficult do you find it to hold the pen stable when injecting insulin?	118	48 (401.7)	14 (11.9)	<0.001
3) How easy/difficult is to hear the clicks for each unit increment?	118	61 (51.7)	9 (7.6)	<0.001
4) How easy/difficult is to feel the clicks for each unit increment?	118	58 (49.2)	8 (6.8)	<0.001
5) How easy/difficult is to push down the injection button?	118	62 (52.5)	14 (11.9)	<0.001
6) How easy/difficult is to turn the dose selector when choosing the right dose?	117	53 (45.3)	3 (2.6)	<0.001
7) How easy/difficult is to know if the push button has been pushed completely down	117	64 (54.7)	9 (7.7)	<0.001
8) How easy/difficult is to see the dose scale when injecting?	117	75 (64.1)	10 (8.5)	<0.001
9) How confident are you that you set the insulin dose correctly every time?	117	42 (35.9)	10 (8.5)	<0.001
10) How confident are you that you inject the correct amount of insulin every time?	117	47 (40.2)	11 (9.4)	<0.001
11) Overall, how confident are you in your management of your daily insulin injections using this pen?	113	54 (47.8)	8 (7.1)	<0.001
12) Overall, how confident are you in controlling your blood sugar level using this pen?	113	39 (34.5)	17 (15.0)	<0.005
13) How suitable is the pen to use in public?	112	51 (45.5)	19 (17.0)	<0.001
14) How confident are you that the air shot has been done correctly?	111	40 (36.0)	11 (9.9)	<0.001
15) How convenient do you find the size of the pen?	113	64 (56.6)	6 (5.3)	<0.001
16) How comfortable do you find the handling of the pen (eg, is it easy to hold, does it fit nicely in the hand, etc)?	113	66 (58.4)	13 (11.5)	<0.001

Users were asked to rate the importance of the individual feature of the pen to ensure that the questions dealt with features were relevant for the patients. All were of great significance, as the rating "very/ rather important" was given by 80% to 99% of patients, depending on the actual feature. For example, 96.0% of patients believed that it was "very/rather important" that the dose scale was easy to read (question 1). Regarding this feature, 99.2% of patients answered that they found the dose scale of the FlexPen "very/fairly easy to read," whereas 68.5% gave this assessment to the Humalog Pen [50].

When asked if they had experienced any problems using the pens, 32.4% answered that they had experienced problems with the Humalog Pen, and 9.0% had experienced problems with the FlexPen ($P < 0.001$). The most frequently reported problems with the FlexPen were various kinds of injection difficulties (8 patients). For the Humalog Pen, this type of problem was also the most frequently reported (23 patients). In addition, several patients found it difficult to read the dose scale of the Humalog Pen (nine patients), and concern was expressed as to whether the correct dose had been injected using this pen (seven patients) [50].

Patients were asked about their pen preference in the comparative questionnaire, completed at the end of the second treatment period (**Figure 3**). For overall ease of use, 73.6% preferred the FlexPen, whereas 9.1% preferred the Humalog Pen ($P < 0.001$). The remaining 16.5% and 0.8% of patients found the devices equally easy or equally difficult to use, respectively. In addition, 74.6% preferred to continue using the FlexPen, and 14.3% favored the Humalog Pen ($P < 0.001$). The remaining 7.1% and 4.0% of patients preferred either or neither device, respectively [50].

Before entering this trial, ~78% of patients had used a device from Novo Nordisk A/S, 14% a device from Eli Lilly and Company/Becton, Dickinson and Company (Eli Lilly/BD) (Eli Lilly devices are produced by BD), 7% a vial and syringe, and 1% a device from other manufacturers. When evaluating pen preference for these groups separately, the results were similar to those of the entire population. Hence, of the Novo Nordisk A/S device users, 73.5% preferred to

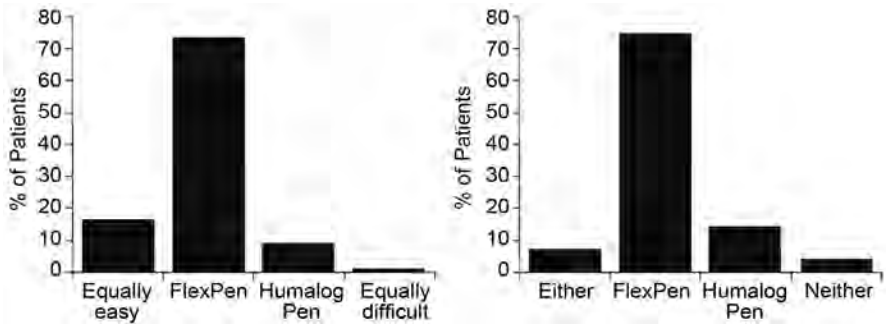

Figure 3. Patients' preference for pen device assessed using the comparative questionnaire. FlexPen vs Humalog Pen, P < 0.001. FlexPen = NovoMix® 30 FlexPen® (Novo Nordisk A/S, Bagsværd, Denmark); Humalog Pen = Humalog®Mix25™ Pen (Eli Lilly and Company, Indianapolis, Indiana) [50].

continue using the FlexPen and 17.4% the Humalog Pen. Of the Eli Lilly/BD device users, 73.7% preferred to continue using the FlexPen and 5.3% the Humalog Pen [50].

Preference for a particular device might be influenced by previous experience; for example, patients might choose a pen from the manufacturer of their previous pen. When patients were grouped by previous pen manufacturer (Novo Nordisk A/S or Eli Lilly/BD), the pen preference in the 2 groups was similar. Hence, of the Novo Nordisk pen users, 73.5% would prefer to continue using the FlexPen and 17.4% the Humalog Pen; of the Eli Lilly/BD users, 73.7% would prefer to continue using the FlexPen and 5.3% the Humalog Pen. Thus, a predetermined preference for pens produced by the patients' previous pen manufacturer was not demonstrated [50].

9. Summary

The results of this study showed that treatment with premixed aspart 30 was non-inferior to treatment with premixed insulin lispro 25. In addition, Self-monitored blood glucose (SMBG) levels were comparable. Safety profiles were similar between both treatments, as was the incidence of hypoglycemic episodes [50].

Moreover, the switch between both products of the low-mix family can be carried out without any problem. The US FDA stated that, in emergency conditions, one insulin mix product might be substituted for another on a unit-per-unit basis [51].

Preference for a particular device might be influenced by the previous experience of the patients. Thus, the results of the previous study of Niskanen *et al*. (2004) were not conclusive as regards this item. Hereunder, we will present some different views from other studies related to the device evaluation. Ignaut *et al*., 2008 in their study, evaluated the ergonomic features and injection force, as measured by the glide force (GF), the glide force variability (GFV) for the new Humalog® Mix75/25 KwikPen™ (KwikPen), and compared with the NovoLog® Mix 70/30 FlexPen® (FlexPen). Fifty prefilled insulin pen devices (25 of each type) were measured for diameter at the cartridge holder and dose window, length and weight with cap attached, and thumb reach at 30 and 60 units. GF was also determined for 100 devices (50 of each type); GFV at 30 and 60 unit doses was calculated for the plateau portion of the force curve based on the minimum and maximum force measured in that portion of the curve [52]. The results of this study showed that, while FlexPen was lighter in weight than KwikPen, and presented a slightly smaller diameter at the cartridge holder and dose window, KwikPen had a shorter overall pen length compared to FlexPen, with a shorter thumb reach at both the 30- and 60-unit dose settings. The maximum GF for KwikPen was less than FlexPen. KwikPen GFV was lower across both doses. They concluded that while FlexPen was lighter with a slightly smaller cartridge holder and dose window diameter, KwikPen was shorter in length with

less thumb reach than FlexPen. KwikPen also demonstrated lower GF and GFV, resulting in a smoother injection profile than FlexPen. These features of KwikPen's design and function may offer important advantages for the user during insulin administration [52].

In another simulated injection study by Ignaut *et al*. (2009) showed patients' preference for Humalog KwikPen to the vial and syringe and FlexPen. Humalog KwikPen was found to be easy-to-use, easy-to-hold while injecting, and easy-to-press the injection button. Accurate dose measurements were reported with Humalog KwikPen more than with vial and syringe. Feature comparison of Humalog KwikPen to vial and syringe found the pen device preferable to vial and syringe in all attributes compared. A pen device may offer greater patient acceptance of insulin therapy and improved treatment satisfaction. These findings may be clinically beneficial because health gains may be obtained through increased adherence and enhanced diabetes self-management. The advantages of pen devices used in this study should be considered by health care providers in consultation with patients regarding diabetes treatment options [53].

A third study was a randomized, open-label, two-period, eight-sequence crossover study in insulin pen-naïve patients with DM was carried out by Clark *et al*. (2010) to determine the patient ease-of-use and preference for the Humalog KwikPenversus the next generation FlexPen. The results of this study showed that among pen-naïve patients with DM who had a preference, the majority preferred the insulin lispro pen over the insulin aspart pen with regard to ease-of-use [54].

10. Recommendations

- Both products of the low-mix premixed insulin analogues aspart 30/70 and premixed insulin lispro 25/75 have comparable efficacy and safety as shown from the medical literature. Therefore, we can change from one to another safely as demonstrated by the US FDA statement.
- In addition, the ergonomic features of KwikPen's design and function may offer important advantages for the user during insulin administration.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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