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Original Article

Improving HbA1c Levels by Methylcobalamin Vitamin in Diabetic Volunteers, Combined with Dapagliflozin as Type 2 Diabetes Mellitus Routine Treatment: A Controlled Randomized, Double-blind Trial

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What's Known

- Dapagliflozin is a glycemic-lowering agent drug used to treat type 2 diabetes mellitus.
- Vitamin B12 is an important vitamin for neurological function and is used in treating memory problems, muscle weakness, and mental disorders.

What's New

- The co-treatment of type two diabetes mellitus with dapagliflozin and vitamin B12 lowered glucose levels significantly compared to dapagliflozin alone. Furthermore, the combination reduced the BMI more significantly.

Abstract

Background: Diabetes mellitus is predominantly a growing global problem interconnected proportionally with obesity escalation. The current study evaluated the prognostic implications of vitamin B12 administration on Body Mass Index (BMI) and glycosylated hemoglobin (HbA1c) levels in type 2 diabetic patients treated with dapagliflozin.

Methods: In this controlled randomized, double-blind trial, 160 patients for each arm were enrolled from July 2022 to June 2023 in Amman, Jordan.; 76 females and 84 males with inclusion criteria of vitamin B12 less than 233 ng/ml, age between 19-76 years, HbA1c range between 6.8-9.1%, and BMI less than 35. Group I received only dapagliflozin 10 mg/daily for a period of 12 months, whereas, group II received vitamin B12 supplements, methylcobalamin 500 µg, once daily with dapagliflozin 10 mg/day. HbA1c, Vitamin B12, and BMI were measured at time intervals of 0, 6, and 12 months. Using SPSS version 23, P values<0.05 were considered statistically significant. The continuous variables were reported as median and IQR. Mann-Whitney-u test and Correlations Spearman's rho were used for continuous variables.

Results: The co-administration of vitamin B12 significantly decreased the levels of HbA1c in group II (54 participants) to 6.66±0.643 by 0.6 %, $F(2,78)=172$, $P<0.001$, compared to the subjects in group I (6.92±0.434). A significant impact of vitamin B12 administration on BMI lowering was observed at different time intervals during the study (P=0.002).

Conclusion: The co-administration of vitamin B12 as a supplement for diabetic patients improved BMI and HbA1c levels.

Trial registration number: NCT06241638.

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Keywords ● Diabetes mellitus ● Glycated hemoglobin ● Vitamin B12 ● Body mass index ● Dapagliflozin

Introduction

Type 2 diabetes mellitus (T2DM) is ultimately a growing global health problem proportionally linked to obesity epidemics.[1] According to the 2021 report of the International Diabetes Federation (IDF), the worldwide prevalence of T2DM in adults is 10.5%, which

accounts for 536.6 million patients.[2] The Middle East and North Africa (MENA) geographical regions have the world's second-highest prevalence of diabetes mellitus (DM). By 2045, the prevalence of T2DM is anticipated to reach 12.8% (54.8 million individuals), an increment of 96% compared to the current statistics.[3] Several national population-based epidemiological studies were conducted between 1994 and 2017 in Jordan (a MENA country), emphasizing a high DM prevalence of 9% to 30%.[3, 4] Jordan's T2DM epidemic is expected to grow significantly over the coming decades to reach regrettably a massive prevalence, despite the efforts implemented to hamper the incidence.[3]

T2DM is considered a burden on countries as the annual cost for a single patient is estimated at 740 USD annually.[5] T2DM results in reduced insulin responsiveness, known as insulin resistance. In this condition, insulin is ineffective at regulating blood sugar levels, so the body initially compensates by producing more insulin to keep blood sugar balanced. However, over time, this increased insulin production becomes insufficient, leading to T2DM. T2DM is most common in people over the age of 45.[6, 7] However, T2DM also affects youth and teenagers, mainly attributed to childhood obesity.[7, 8]

The most common complication is neuropathy with a distal symmetric polyneuropathy of limbs.[9] At least 50% of diabetics acquire diabetic neuropathy over time,[9] and it can cause devastating symptoms such as unbearable and unrelenting pain, as well as severe life-threatening outcomes such as "diabetic foot".[10]

Dapagliflozin, the main ingredient in Forxiga (an anti-glycemic drug), inhibits sodium-glucose cotransporter 2 (SGLT2) protein in the kidney nephrons.[11] SGLT2 protein is responsible for reuptaking glucose from urine into the bloodstream while the blood is filtered in the kidneys.[12, 13] Dapagliflozin reduces blood glucose levels by inhibiting the function of SGLT2 in the kidneys and consequently lowers the levels of glycosylated hemoglobin (HbA1C). The total amount of glucose eliminated by the kidney via this process is determined by the blood glucose levels of the glomerular filtration rate (GFR).[11, 14] Thus, in people with normal blood glucose along with low GFR, dapagliflozin has a low proclivity to produce hypoglycemia since the amount of filtrated glucose is modest and may be reabsorbed by the SGLT1 and unblocked SGLT2 transporters.[15]

Cobalamin (Cbl), commonly known as B12 (vitamin B12 or vit. B12), is a water-soluble molecule essential for life.[15] They are essential for the body's anabolic and catabolic processes, with an emphasis on powerful cell replicative processes such as hematopoiesis and tissue expansion. Additionally, Cbl plays an important role in neuronal health. It supports the normal function of Cbl and is needed for red blood cell formation and DNA synthesis.[16]

Growth and development seen in children may necessitate extra B12, which is involved in muscle and tissue growth and may diminish circulating B12 levels. Individual variances in genetic and physiological factors can result in variable rates of B12 turnover and absorption. Adherence to dosing regimens is important, as irregular dosing in younger individuals may interfere with expected increases in B12 levels. Finally, compelling health conditions and underlying genetic factors may differentially affect B12 absorption and intake by age.[17]

Methylcobalamin (MeCbl) belongs to the category of pure vitamin B12.[16] The medicine is prescribed for treating vitamin B12 deficiency and pernicious anemia.[16] The medicine is manufactured by Eisai in Japan. Although it is an over-the-counter medicine, it is advised to consume the medicine after consulting a medical practitioner.[16] This eliminates the risk of possible interactions with other medications and the side effects of high-intake doses. The medicine contains MeCbl as its main ingredient and has gained market share in nutritional formulations.[10] Essentially, the implications associated with Cbl deficiency including hypoproteinemia are counteracted by MeCbl therapy.[10] It is an effective treatment for the majority of common ailments, including cardiovascular disease, diabetes, anemia, hyperhomocysteinemia, and degenerative disorders. MeCbl aids in the production of neuronal lipids and the regeneration of axonal nerves and has a neuroprotective effect, which promotes correct neuronal function.[18]

Vitamin B supplements such as B12 and folic acid have shown a potent implication on glycemic levels in non-insulin-dependent diabetic patients. Furthermore, clinical studies highlighted the significant effect of B12 in confronting the hurdles of neuropathy and megaloblastic anemia.[19]

The gold standard for measuring glycemic management is HbA1c. HbA1c is also known as A1c.[20] In the body, proteins chemically react with glucose and become glycosylated. HbA1c measures average glycemia during the past 6-8 weeks.[20, 21] HbA1c is not only a reliable marker of chronic hyperglycemia, but it also corresponds well with the risk of long-term diabetic complications. Because of the useful information offered by a single HbA1c test, it has become a solid biomarker for diabetes diagnosis

and prognosis. The HbA1c test is currently recommended as a standard of care (SOC) for assessment and surveillance of T2DM.[22]

In the current study, we will explore the prognostic effect of co-administration of vitamin B12 with dapagliflozin in T2DM patients over a period of 12 months. The outcomes of body mass index (BMI), HbA1C, and vitamin B12 levels will be measured during the study period of 12 months at a time interval of every 3 months. The implications of administration of vitamin B12 with dapagliflozin on HbA1c levels as well as the BMI will be investigated.

Patients and Methods

Study Design

A prospective randomized controlled trial was carried out over a period of one year in the Faculty of Pharmacy and Medical Sciences at Petra University- Jordan between July first, 2022, and 30 June 2023. A total of 160 volunteers, including 86 male and 74 female patients aged between 19-76 years with reported T2DM and treated with dapagliflozin as a routine medication for their case participated in the current study.

Randomization and Allocation

At the beginning of the convenient sampling phase, study individuals were randomized to either Group I was treated with dapagliflozin 10 mg once daily, and other study individuals were randomly assigned to Group II were treated with dapagliflozin 10 mg and methylcobalamin 500 mg once daily. All was done by the study investigators. Investigators used a randomly generated randomization protocol, which was 1:1 (dapagliflozin/ dapagliflozin, Forxiga) 10 mg (AstraZeneca, UK) and Methylcobal (Eisai, Japan) (500 mg once daily) and was blocked for all 80 subjects.

Randomization/allocation cover-up was done by study investigators: double-blinded medications were allocated using number-labeled drug boxes. Hid medication allocation was done by study investigators, which protected blinding during a one-year trial.

Blinding of the study: Patients and researchers were blinded to the identity of the study group I and II. Patients and investigators did not know each other during the whole study period. Blinding was done throughout the one-year study period.

Outcomes of the study: Primary outcome: Comparison of the baseline-adjusted differences in HbA1c between Group I was treated with dapagliflozin 10 mg once daily whereas Group II was treated with dapagliflozin 10 mg and MeCbl 500 mg once daily at the end of this trial.

The study with their proper written consent and permission from the Institutional Ethical Committee of Mutah University SREC-2022/783. The study was registered at ClinicalTrials.gov No. NCT06241638. As per inclusion criteria, newly diagnosed and known cases of type 2 diabetics with glycated hemoglobin in the range of 6.8%-9.1%, ages between 18 to 75 years, and BMIs less than 40 were selected for the study. However, no pregnant women or cancer patients were included in this study. The study duration was 12 months, and the HbA1c was measured at the start of this study with other parameters such as BMI and vitamin B12 level. The study population was divided into two groups; Group I was treated with dapagliflozin 10 mg once daily whereas Group II was treated with Dapagliflozin 10 mg and MeCbl 500 mg once daily, and both groups were enrolled in the study for 12 months. At the beginning of the study, the baseline readings of vitamin B12, BMI, and HbA1c were measured, and every 3 months, a new measurement was conducted to explore the impact of vitamin B12 administration on BMI and HbA1C levels in dapagliflozin-treated diabetic patients.

Instruments

Analysis of vitamin B12 was done by using second generation Cobas e411analyzer, (Electro-chemo-luminescence [ECL] technology, Roche Elecsys, Germany). A 60 µL sample was added to the standard Hitachi cup150 tube UI (Hitachi, Japan). The 60 µL sample volume was approved by the institutional review committee and as per the guidelines of a governmental agency. A signed consent form for each subject enrolled in this study was taken. The implemented variables included age, gender, BMI, medical history, vitamin B12 supplements if intake, and symptoms such as poor memory, depression, fatigue, and cold hands. Blood samples of 3-5 mL were collected in tubes and then separated by centrifugation, the serum was collected in labeled tubes and stored at -20 °C until the analysis. A 250 µL serum of each sample was transferred to the cuvette of the Cobas e411 analyzer. Vitamin B12 concentration in human serum was determined by a vitamin B12 kit (Cobas, Roche, Germany) as per manufacturer procedures. The kit works based on the principle of competitive binding.

The i-Chroma reader (Bodntech, Korea) is a first-generation portable fluorescent scanner that analyzes blood, urine, and other samples and displays measurement results on the screen. Furthermore, the i-Chrom Reader is an immunoassay system for the quantitative measurement of HbA1c in human blood.

The test is used for routine monitoring of the long-term glycemic status in patients with DM. The incubator (i-Chamber, Biolab, Italy) is an Incubation chamber for testing HbA1C.

Cartridge (kits) for measuring the concentration of HbA1c in biological liquid samples (Serum) (Accu-Chek products, Roche, USA).

Sodium Citrate Buffer

Hemolysis buffer (Roche, Germany) composed of a cationic detergent (stable for up to 20 months if stored at 4 -30 °C) was pre-dispensed individually in a small tube.

The detection buffer contains fluorescence-labeled HbA1c-peptide, fluorescence anti-rabbit Immunoglobulin G (IgG), Bovine serum albumin (BSA, PluriSelect, Germany) as a stabilizer, and sodium azide (Alpha Chemica, India) as a preservative in Phosphate-buffered saline (PBS), and is stable for up to 20 months. Allow the detection buffer to reach room temperature (20-30 °C) before starting a test.

Protocol

Dapagliflozin 10 mg (Forxiga, film-coated tablet, AstraZeneca, UK Limited/United Kingdom) and methycobal 500 µg (Mecobalamin tablet, Eisai, Japan) were used.

Inclusion criteria include; age between 19-76 years, male and female HbA1c>6.8%, serum vitamin B12 level <223 pg/mL. Exclusion criteria include pregnant, lactating mother patients with insulin-dependent DM, severe and complicated diabetes, and patients with hepatic or renal dysfunction. Baseline investigations were carried out for all enrolled participants at Alhakam Laboratory-Rusaifa (Accredited laboratory). The drug group received methylcobalamin 500 µg once daily with their usual anti-diabetic therapy. The control group received suitable anti-diabetic drug therapy dapagliflozin 10 mg daily. Methylcobalamin 500 µg was given for a period of 12 months and was followed up at 4 weeks. All investigations were carried out at the beginning of the study.

Statistical Analysis

In this study, continuous variables were reported as median and IQR. Mann-Whitney-u test and Correlations Spearman's rho were used for continuous variables. Categorical variables were reported as a number and percentages. Moreover, the Chi square test was used to test the difference in the categorical outcome variables. A generalized estimating equations model was used to analyze the data obtained in this study during time. Data were analyzed using SPSS 23 (IBM, USA), and P values<0.05 were considered statistically significant.

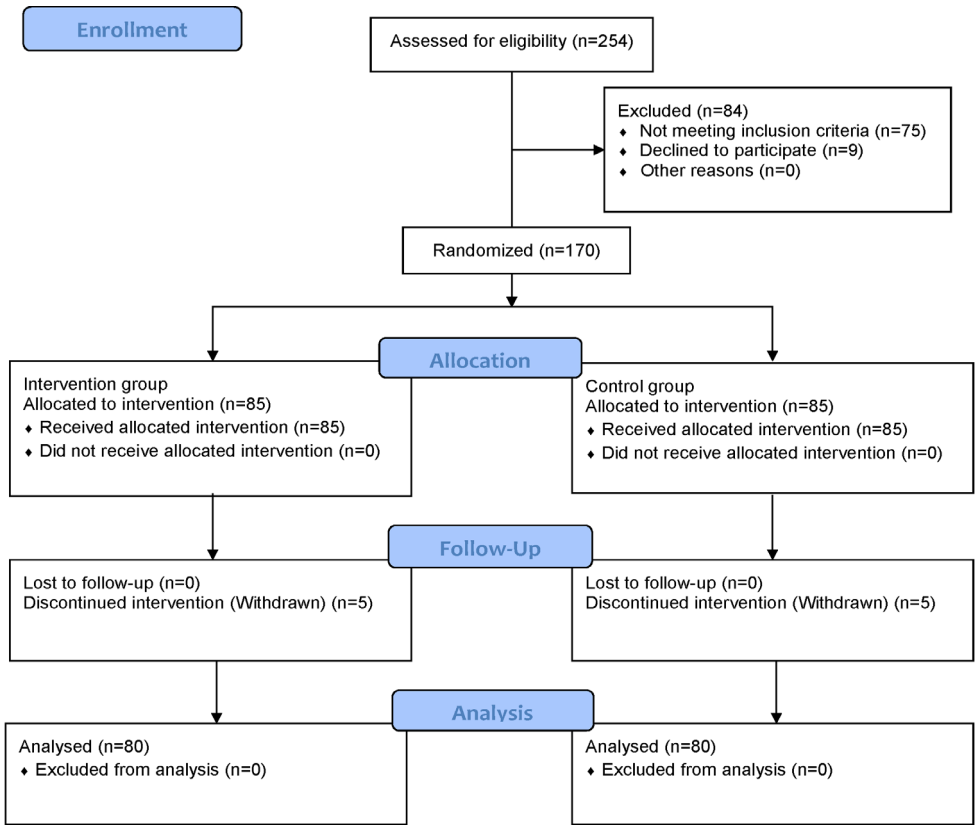

Figure 1: Flow chart of the randomized controlled trial (RCT) is depicted.

Table 1: The baseline characteristics of the demographic data and biochemical levels among the study groups I and II

Variables		Dapagliflozin	Dapagliflozin+vitamin B12	P value
		n=80	n=80	
Age (years)		52.5 (42.25-67)	52.5 (43-64)	0.916
Sex	Male	44 (%55)	40 (%50)	0.527
	Female	36 (45%)	40 (50%)	
BMI (Kg/m2)		28.2 (27.2-30.37)	28.7 (27-30.1)	0.822
Vitamin B12 (ng/ml)		194.5 (184.2-204)	196.5 (187.25-207.75)	0.095
HbA1c %		7.9 (7.5-8.27)	7.7 (7.4-8.2)	0.27

Student-independent *t* test was conducted to investigate the demographic variation between the control group (dapagliflozin) and the test group (dapagliflozin+Vitamin B12). There was no significant difference between the two groups at the beginning of the study.

Results

A total of 254 T2DM patients treated with dapagliflozin were randomly chosen to participate in the current study (figure 1). 160 participants divided into two groups completed the 12-month study, whereas 84 participants were excluded majorly for not meeting the inclusion criteria, and 10 participants discontinued the study.

The demographic data and baseline biochemical findings in groups one and two were summarized in (table 1), there was no significant difference between the values of groups one and two at the beginning of the current study.

The study groups had ages ranging from 19 to 79 years with a mean of 52.3±16.1, and the BMI for the participants ranged from 25 to 33 with a median of 28.7±2.23 (table 1). The HbA1c range was from 6.8 to 9.1, and the mean was 7.88±0.62, while vitamin B12 levels ranged from 146 to 233 ng/mL with a mean of 195.85±19.1 ng/mL. The treatment of diabetic patients with dapagliflozin and methylcobalamin significantly decreased HbA1c levels to 6.66±0.64, $F(2,78)=172$, $P<0.001$, within 12 months (figure 2) compared with the treatment of diabetes with dapagliflozin alone, in which HbA1c level was 6.92±0.43. The levels of HbA1c reduced significantly after 3 months of treatment with vitamin B12 and dapagliflozin ($P=0.009$) (supplement1), and the decrease in HbA1C levels was continuous during the study period until the study was terminated at 12 months (figure 2). Likewise, the administration of dapagliflozin with B12 lowered BMI to 27.28±5.98, $P=0.045$, whereas, the administration of dapagliflozin alone reduced the BMI for the participants to 28.14±3.71 (figure 3). The administration of methylcobalamin for 12 months raised the B12 level to 343.8±70.25 ng/mL ($P<0.001$) for group II participants ($F(2,78)=3669$, $P<0.001$) (figure 4). Spearman rho correlation analysis revealed a significant decrease in the BMI level with age after the administration of vitamin B12 ($r=0.341$, $P=0.002$).

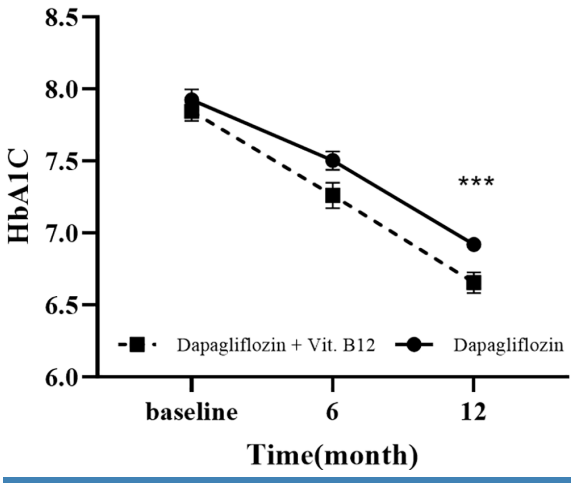

Figure 2: Changes in the biochemical levels of the HbA1C parameter of the two study groups after the administration of oral medications at different time intervals. Group I received dapagliflozin 10 mg alone whereas group II received dapagliflozin 10 mg and vitamin B12 500 mg. There was a significant time effect on the glycated hemoglobin between the two groups at the time point of 12 months. Time effect<0.001, Time group=0.147, Group effect=0.020. ***P<0.0001 considered significant between groups by Bonferroni correction.

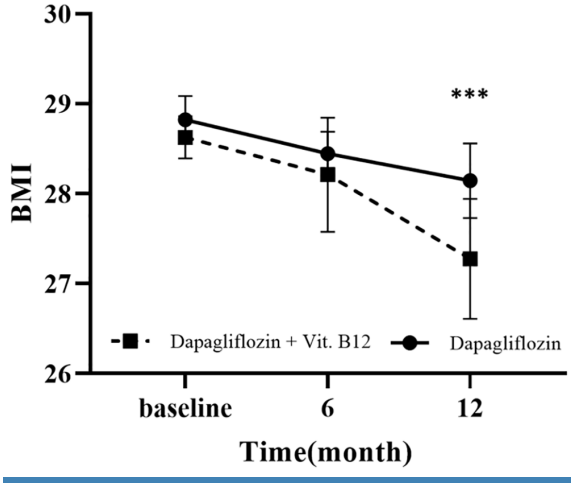

Figure 3: Changes in the biochemical levels of BMI parameter of the two study groups after the administration of oral medications at different time intervals. Group I received dapagliflozin 10 mg alone whereas groups II received dapagliflozin 10 mg and vitamin B12 500 mg. There was a significant time effect on the body mass index between the two groups at the time point of 12 months, Time effect<0.001, Time group=0.028, Group effect=0.456. ***P<0.0001 considered significant between groups by Bonferroni correction.

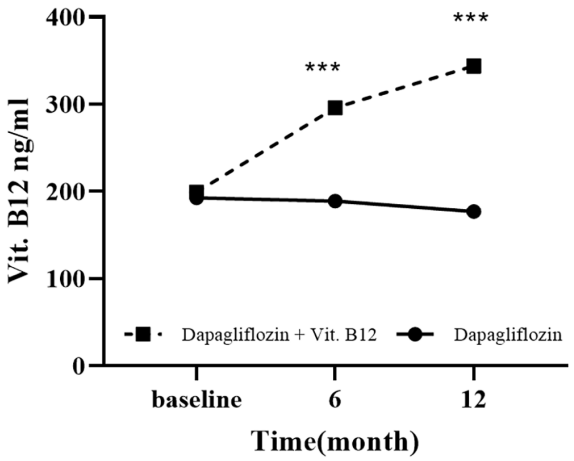

Figure 4: Changes in the biochemical levels of vitamin B12 parameter of the two study groups after the administration of oral medications at different time intervals. Group I received dapagliflozin 10 mg alone whereas group II received dapagliflozin 10 mg and vitamin B12 500 mg. There was a significant time effect on the vitamin B12 levels between the two groups at the time point of 6 and 12 months. Time effect<0.001, Time group<0.001, Group effect<0.001. ***P<0.0001 considered significant between groups by Bonferroni correction.

A significant decrease in HbA1c levels (r=0.285, P=0.010) was associated with the administration of vitamin B12 for a period of 6 and 12 months. There was a significant reciprocal impact of vitamin B12 level on BMI readings, as there was a significant decrease in BMI levels when vitamin B12 was administered daily (r=-0.243, P=0.03). The BMI levels were higher in males than females (r=0.299, P=0.007), whereas, significantly lower levels of vitamin B12 were demonstrated in males than in females, and higher HbA1c levels were noted at 187.7±19.79 versus 195.3±18.35, P=0.034, respectively. Additionally, a significant association between BMI and vitamin B12 levels in group I was demonstrated, as there was a significant decrease in B12 levels during the study duration (r=-0.247, P=0.027).

There was a significant effect of the time on the two study groups. as there was a significant difference between the levels of the study parameters, including BMI, vitamin B12, and glycated hemoglobin levels, at the beginning of the study and after 12 months (P=0.028) (figure 3). Both parameters of BMI and vitamin B12 showed a significant difference between the study groups and the time (P<0.001), whereas there was no significant difference between the HbA1c levels in the two study groups (P=0.147) (figure 4). There was a significant group effect of vitamin B12 administration on HbA1c levels during the study duration (P=0.02) (figure 2).

Discussion

In the current study, the clinical treatment of diabetic patients with dapagliflozin alone reduced both the weight and glycemic parameters during the study duration. Whereas, an exponential significant decrease in weight and glycemic levels (P<0.05) was observed when a supplement of vitamin B12 was included in the treatment strategy.

A positive correlation between B12 levels and HbA1c titers after 3 months of B12 supplementation of 32.4% (P=0.003) was observed, indicating a subtle tendency for people with higher B12 ranges to present decreased HbA1c levels by the co-administration of vitamin B12 supplements. This correlation continued at various time points, including after 6 and 9 months and one year of B12 supplementation, emphasizing the sustained impact of B12 supplementation on blood sugar manipulations.

The co-administration of vitamin B12 in diabetic patients overcomes the condition of megaloblastic anemia in an interval time of 3 months, which ameliorates HbA1c levels by 0.94 mg/dL. Potential mechanisms behind these observations include the enhancement of insulin sensitivity and the reduction of inflammation, both of which contribute to higher blood sugar regulation and decreased HbA1c stages.[17, 23]

The current study emphasizes a robust reciprocal correlation between HbA1C and vitamin B12 of 52.7% (P<0.001), indicating that people with better B12 levels tend to show lower HbA1C levels. The probable factors for this correlation include B12 ability to enhance insulin sensitivity and reduce infection, as well as the impact of nutrition and lifestyle.[17, 23]

A significant positive correlation was demonstrated between gender and BMI (29.9%; P=0.007), indicating that, on average, men have slightly higher BMI values than females. Similar to our results, Bredella showed differences in the in-body composition, with males having a greater proportion of dense muscle mass. Additionally, the distribution of fats, particularly across the abdomen, differs between genders, influencing differences in average BMI.[24]

Additionally, a negative correlation between gender and vitamin B12 levels was seen (38.6%; P<0.001), with females, on average, displaying higher vitamin B12 ranges than men. Similar to our results, Margalit and colleagues showed that men in the general population are susceptible to vitamin B12 deficiency. Neither diet nor estrogen effects can account for this.[25] Additionally, Xu and colleagues reported decreased homocysteine ranges in females.[26] Moreover, a reciprocal correlation was demonstrated between B12 absorption and hyperhomocysteinemia in our bodies.[18]

Moreover, a positive correlation was located between gender and HbA1C levels (27.7%; P=0.015), with males having a slightly greater increase of HbA1C levels than females in common. Consistent with the findings of a previous study by De Paoli and colleagues, this suggests these elevations may be due to several factors, including low ranges of sex hormone-binding globulin (SHBG) and hormones such as testosterone and estrogen, which play a role in those variations.[27] Additional findings from a previous study by Eliasson and colleagues also proved factors such as smoking, affect insulin resistance and are intently related to the HbA1C range in men.[28]

One of the influential factors in the current study was the age of participants as numerous health parameters were affected by the increase in age. A significant positive correlation between age and BMI (47.4%; P<0.001) was observed, indicating that as people age, their BMI increases proportionally. A study conducted by Meeuwsen and colleagues in the United Kingdom on a population of 23,627 adults aged between 18 and 99, reported a progressive positive correlation between age and BMI.[29] In particular, our data match with the findings of Kıskaç and colleagues, showing a probability that this positive correlation may be attributed to decreased physical activity and much less healthy dietary habits.[30] Although Pataky and colleagues also found that it is due to age-related metabolic changes and hormonal fluctuations.[31]

Furthermore, the current study also demonstrated a moderately positive correlation between age and B12 levels after one year of B12 supplementation (P=0.002). Surprisingly, significantly lower levels of vitamin B12 was noticed in young participants than in the older group (P<0.05). This phenomenon could be caused by several interconnected variables. Younger people have faster metabolic rates and higher levels of physical activity, which results in increased energy expenditure and a higher requirement for B12 in cellular activities.[32] They may have varied dietary habits and preferences. For example, younger people may consume foods that aid B12 absorption, whereas older people may adhere to dietary restrictions.[32] Finally, compelling health conditions and underlying genetic factors may differentially affect B12 absorption and intake by age.[17]

Similarly, we determined a weak negative correlation between age and HbA1c stages 3 months after administration of vitamin B12 supplement (r=-23.2%, P=0.039). Several factors may contribute to this clinical finding, including the potential effects of metabolism, B12 absorption, and lifestyle choices among older people. Faster metabolic rates and higher B12 levels may affect glucose metabolism, potentially leading to better blood glucose control. Simultaneously, vitamin B12, which plays an important role in metabolic processes, helps in the effective breakdown of carbohydrates into glucose.[17] The link extends to insulin sensitivity, with B12 deficiency linked to insulin resistance. Improved B12 levels may promote the body's reactivity to insulin, allowing cells to absorb glucose more efficiently. Furthermore, the observed relation may be influenced by the overall impact of lifestyle choices, as frequent physical activity, which is commonly practiced by younger people, synergizes with B12 supplementation to improve glucose metabolism.[17, 23]

Our research revealed a negative correlation between BMI and B12 levels (r=-0.24.3, P=0.030). Generally, individuals with a higher BMI tend to have lower B12 tiers.[33, 34] Previous research on the relationship between serum vitamin B12 levels and adult obesity suggested a significant negative impact of vitamin B12 levels on obesity.[35] Our findings support the prior research that showed the inverse relation of serum vitamin B12 levels with obesity.[35] This connection may be attributed to factors such as insulin resistance, the presence of clinical conditions e.g., atrophic gastritis, medication use, and dietary habits that impair B12 absorption.[17]

Another noteworthy finding was a significant correlation between BMI and HbA1c ranges 3 months after taking a B12 supplement (r=-0.282, P=0.011). Vitamin B12 administration vigorously lowered both the glycemic and the weight indicators in a dose-dependent manner. Higher BMI values are frequently associated with greater adipose tissue, which is active in metabolism and can release inflammatory chemicals, thereby impacting insulin resistance and, as a result, HbA1c levels.[4, 17, 36] The significance of B12 in affecting insulin sensitivity as well as glucose metabolism adds another layer of depth to this interaction. B12 supplementation could interfere with BMI-related metabolic pathways, altering the observed connection.

The current study had some limitations, since the participants' medical profiles were not fully controlled, and parameters such as kidney function and glomerular filtration rate were not included in the study. Additionally, the factors of physical activity and food intake behavior were not included.

Conclusion

The current study emphasizes the

co-administration of vitamin B12 supplement for diabetic patients under treatment with dapagliflozin can improve their BMI and glycemic parameters.

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Authors' Contribution

W.A: Study design, Data interpretation, and reviewing the manuscript; Z.Z: Data gathering and drafting the manuscript, M.H: Study concept, data interpretation, and reviewing the manuscript, IS.M: Data gathering, and reviewing the manuscript; W.AD: Data interpretation and drafting the manuscript; N.S: Study concept and reviewing the manuscript; H.A: Study design, Data interpretation, and reviewing the manuscript; A.Kh: Data gathering, and reviewing the manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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