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Neutrophil to Lymphocyte ratio is significantly reduced after Sodium glucose cotransporter-2 inhibitor treatment in patients with type 2 diabetes mellitus

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Abstract. ***Background.*** *Sodium glucose cotransporter-2 inhibitors (SGLT2i) are novel therapeutic agents that became available in the treatment of type 2 diabetes mellitus (T2DM). This group of antidiabetic agents are associated with reduced glycated hemoglobin (HbA1c), fasting glucose, body weight and body mass index (BMI) in diabetic patients. All those beneficial effects may also be associated with a reduction in inflammatory burden.* ***The purpose*** *of the study is to compare neutrophil to lymphocyte ratio (NLR), a novel inflammatory marker derived from hemogram, before and 6 months after SGLT2i treatment in diabetic subjects. We also aimed to compare fasting glucose, HbA1c and other metabolic parameters as well as anthropometric measures (weight, BMI) before and 6 month after initiation of SGLT2i therapy.* ***Materials and methods.*** *The subjects with type T2DM that show up in internal medicine outpatient clinics of Abant Izzet Baysal University Hospital between January 2021 and December 2021 were enrolled to the study. Pretreatment and posttreatment NLR and other parameters were compared. We also obtained pretreatment and posttreatment laboratory data including urea, creatinine, fasting glucose, HbA1c, glomerular filtration rate, aspartate and alanine transaminases, plasma sodium and potassium.* ***Results.*** *Fasting glucose was reduced from 195 ± 72 mg/dl in pretreatment period to 146 ± 53 mg/dl in posttreatment period ($p < 0.001$). HbA1c was reduced from 9.1 ± 1.7 % in pretreatment period to 7.7 ± 1.7 % in posttreatment period ($p < 0.001$). The NLR before treatment was 2.6 ± 1.2 % before SGLT2i treatment and was reduced to 2.2 ± 0.6 % in 6th month of SGLT2i therapy. NLR was significantly decreased after treatment ($p = 0.003$).* ***Conclusions.*** *We suggest that NLR levels could be a marker of reduced inflammatory burden in T2DM subjects receiving SGLT2i treatment.*

Keywords: *type 2 diabetes mellitus; inflammation; neutrophil to lymphocyte ratio; sodium glucose cotransporter-2 inhibitor; fasting glucose; HbA1c*

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder associated with significant morbidity and mortality. Mild but persistent inflammation has an important place in the course of T2DM. Indeed, several inflammatory markers derived from routine hemogram tests were suggested to be associated with T2DM [1–6], and with its complications [7–11]. Effective treatment of the diabetic subjects may reduce the inflammatory burden in this population.

Sodium glucose cotransporter-2 inhibitors (SGLT2i) are novel therapeutic agents that became available in the treatment of T2DM. This group of antidiabetic agents are associated with reduced glycated hemoglobin (HbA1c), fasting glucose, body weight and body mass index (BMI) in diabetic patients [12]. All those beneficial effects may also be associated with a reduction in inflammatory burden.

To test this hypothesis, we designed the present study to compare neutrophil to lymphocyte ratio (NLR), a novel inflammatory marker derived from hemogram, before and 6 months after SGLT2i treatment in diabetic subjects. We also aimed to compare fasting glucose, HbA1c and other metabolic parameters as well as anthropometric measures (weight, BMI) before and 6 month after initiation of SGLT2i therapy.

Materials and methods

Study Design. Patients who were followed up in our internal medicine outpatient clinics and were treated with SGLT2i between January 2021 and December 2021 were included in

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the present retrospective study. Local ethics committee was approved the study (ethics approval no: 2021/233). Those under the age of 18, those with end-stage renal disease, those with active infection or inflammatory disease, and those receiving cancer treatment were excluded from the study. Age and gender of the participants recorded. Anthropometric measures; body weight and BMI before and at the sixth moth after SGLT2i treatment were recorded. We also obtained pretreatment and posttreatment laboratory data including urea, creatinine, fasting glucose, HbA1c, glomerular filtration rate (GFR), aspartate and alanine transaminases (AST and ALT), plasma sodium (Na) and potassium (K). The data at least sixth moth after initiation of SGLT2i treatment was recorded as posttreatment data.

Statistical analyses. All data was analyzed by statistics software (SPSS 16.0 for Windows, IBM Co., Chicago, IL, USA). One sample t test was used for analysis of data in whole study population. Variables before and after SGLT2i treatment were analyzed by paired samples t test. The p values lower than 5 % was considered as statistically significant.

Results

Study population was consisted of remaining 78 patients (67 men and 17 women) after exclusion of 11 subjects according to the exclusion criteria. Mean age of the study cohort was 58,7 ± 8,6 years, respectively.

There were no significant differences between pretreatment and posttreatment levels of creatinine, GFR, Na, and K levels ($p > 0.05$ for all).

Body weight ($p < 0.001$), BMI ($p < 0.001$), AST ($p < 0.001$), and ALT ($p < 0.001$) levels were significantly reduced in posttreatment period compared to the pretreatment period. Fasting glucose was reduced from 195 ± 72 mg/dl in pretreatment period to 146 ± 53 mg/dl in posttreatment period ($p < 0.001$). HbA1c was reduced from 9.1 ± 1.7 % in pretreatment period to 7.7 ± 1.7 % in posttreatment period ($p < 0.001$). Figure 1 shows the reduction in study variables.

The NLR before treatment was 2.6 ± 1.2 % before SGLT2i treatment and was reduced to 2.2 ± 0.6 % in 6th month of SGLT2i therapy. NLR was significantly decreased after treatment ($p = 0.003$). Figure 2 shows the change in NLR levels between pre- and posttreatment periods.

Discussion

Present study showed that SGLT2i treatment reduces inflammatory burden related to T2DM. Moreover, the results of present study suggested the previous studies in literature that reported significant decrease in weight, BMI, fasting glucose and HbA1c with SGLT2i treatment.

Besides type 2 diabetes mellitus is a metabolic disorder, significant amount of inflammatory burden has been reported in this condition. An anti-inflammatory cytokine, omentin, has been suggested to be low in insulin resistance states in the medical literature [13]. Another inflammatory cytokine, neuregulin, has been reported to be decreased in T2DM [14], and in diabetic kidney injury [15]. Moreover, inflammatory cytokines, such as cardiothrophin, was shown to be increased in subjects with T2DM [16]. These findings suggest that inflammation involve in the course of T2DM and its complications. The results of the present study were also suggested that effective treatment with SGLT2i may reduce inflammatory burden in this population.

Other metabolic and inflammatory markers have been suggested to be associated with T2DM. Authors reported increased uric acid/HDL cholesterol ratio in diabetic subjects compared to the healthy population [17]. In addition, elevated uric acid/HDL cholesterol ratio has been shown in subjects with metabolic syndrome, another insulin resistant state [18]. Interestingly, SGLT2i treatment was suggested to reduce serum uric acid levels, which is a marker of inflammation and deteriorated metabolism in diabetic subjects [19]. In accordance to the literature data, we showed that SGLT2i treatment lowered NLR levels which reflects underlying inflammatory burden.

Our study also showed reduced fasting glucose and HbA1c levels after initiation of SGLT2i treatment. Previous studies were also reported significant improvement in those metabolic markers in diabetic subjects after SGLT2i therapy [12, 20, 21]. Effective glucose lowering effect of SGLT2i is well established. Significant weight and BMI reduction also contributes to improvement of metabolic parameters in diabetic subjects received SGLT2i treatment. The findings of present study which reported improved weight, BMI, glucose and HbA1c levels, were in accordance with the literature knowledge.

We also found significantly reduced AST and ALT levels after SGLT2i treatment in present work. Although insig-

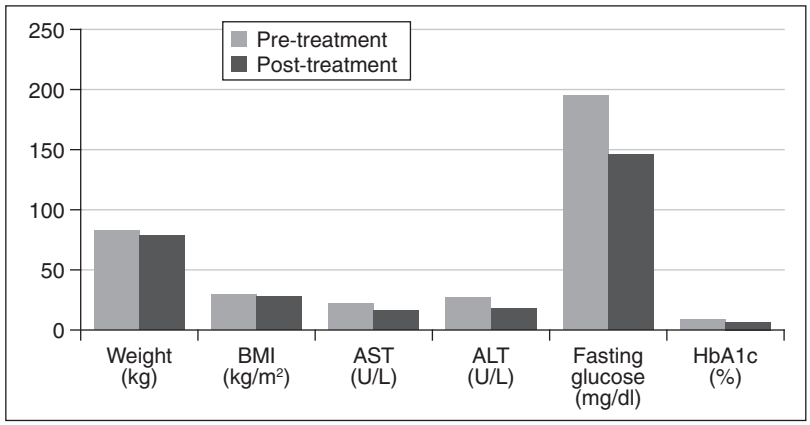

Figure 1. Change in the pre-treatment and post-treatment periods of body weight, BMI, AST, ALT, fasting glucose and HbA1c

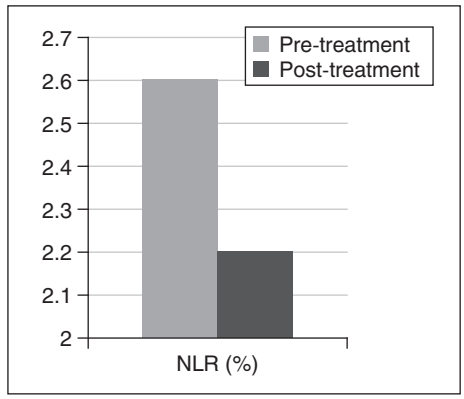

Figure 2. Change in the NLR levels between pre-treatment and post-treatment periods

nificant, reduced AST and ALT levels have been reported in a recent study [12]. Deteriorated metabolism may cause non-alcoholic fatty liver disease in diabetic subjects which is characterized with elevated transaminases. SGLT2i related improvement in metabolism may also cause a reduction in fat accumulation in liver resulting decreased AST and ALT levels. This phenomenon has been suggested by a recent work in the medical literature [22].

Retrospective design and relatively small study population are possible limitations of the present work. We just followed the subjects for six months, which may constitute the third limitation. However, to the bet of our knowledge present study is the first report in the literature showed reduced NLR levels after SGLT2i treatment in patients with T2DM.

Conclusions

In conclusion, we suggest that NLR levels could be a marker of reduced inflammatory burden in T2DM subjects receiving SGLT2i treatment. Further longitudinal studies with larger cohort are needed to confirm our results.

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Вірогідне зниження співвідношення вмісту нейтрофілів і лімфоцитів на тлі лікування інгібіторами натрійзалежного котранспортера глюкози 2-го типу у пацієнтів з цукровим діабетом 2-го типу

Резюме. ***Актуальність.*** Інгібітори натрійзалежного котранспортера глюкози 2-го типу (іНЗКТГ-2) — нові терапевтичні засоби, доступні для лікування цукрового діабету 2-го типу (ЦД2). Ця група протидіабетичних засобів асоціюється зі зниженням глікованого гемоглобіну (HbA1c), глікемії натще, маси тіла та індексу маси тіла (ІМТ) у пацієнтів з ЦД2. Усі ці сприятливі ефекти також можуть бути пов'язані зі зменшенням запалення. ***Метою*** дослідження є порівняння отриманого з гемограми співвідношення нейтрофілів і лімфоцитів, нового маркера запалення, до та через 6 місяців після лікування іНЗКТГ-2 у пацієнтів з ЦД2. Крім того, завданням дослідження було порівняти рівень глікемії натще, глікованого гемоглобіну та інші метаболічні параметри, а також антропометричні показники (маса тіла, ІМТ) до та через 6 місяців після початку терапії іНЗКТГ-2. ***Матеріали та методи.*** Під спостереженням перебували пацієнти з ЦД2 у клініці внутрішніх хвороб університетської лікарні Abant Izzet Baysal у період з січня по грудень 2021 року. Порівнювали співвідношення нейтрофілів і лімфоцитів до та після лікування та інші параметри. Також були отримані лабораторні дані до та після лікування, включаючи вміст сечовини, креатиніну, глікемію натще, HbA1c, швидкість клубочкової фільтрації, аспартат- і аланінтрансамінази, натрій і калій плазми. ***Результати.*** Рівень глікемії натще знизився з 195 ± 72 мг/дл у період до лікування до 146 ± 53 мг/дл у період після лікування ($p < 0,001$). Відзначалося вірогідне зниження рівня HbA1c: з 9,1 ± 1,7 % у період до лікування до 7,7 ± 1,7 % у період після лікування ($p < 0,001$). Співвідношення нейтрофілів і лімфоцитів до лікування становило 2,6 ± 1,2 % і вірогідно знижувалося до 2,2 ± 0,6 % на шостому місяці терапії іНЗКТГ-2. Співвідношення нейтрофілів і лімфоцитів вірогідно зменшилося після лікування ($p = 0,003$). ***Висновки.*** Автор припускає, що співвідношення рівнів нейтрофілів і лімфоцитів може бути маркером зниження запального навантаження у пацієнтів з ЦД2, які отримують лікування іНЗКТГ-2.

Ключові слова: цукровий діабет 2-го типу; запалення; співвідношення нейтрофілів і лімфоцитів; інгібітори натрійзалежного котранспортера глюкози 2-го типу; глікемія натще; глікований гемоглобін