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ORIGINAL PAPER

DIAGNOSTIC VALUE OF A COMPLETE BLOOD COUNT IN TYPE 2 DIABETES MELLITUS AND COMORBIDITIES

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Abstract

Introduction. Diabetes mellitus is associated with overweight and pancreatitis. To date, the results of routine laboratory tests are not being utilized as reliable markers for comorbidities associated with type 2 diabetes mellitus (T2DM).
The objective of the study. The aim of this study was to analyze complete blood count parameters in order to determine significant predictors of T2DM comorbid course.
Material and methods. The study involved 579 T2DM patients with comorbid overweight/obesity and chronic pancreatitis (CP). Complete blood count (CBC) was performed using a Yumizen H500 CT automatic hematology analyzer. Insulin levels were determined using a standard kit with a Thermo Scientific Multiskan FC enzyme-linked immunoassay analyzer. Glucose levels were determined using a standard kit with a COBAS INTEGRA® Diagnostics automatic biochemical analyzer. The neutrophil-to-lymphocyte ratio (NLR) was calculated based on CBC.
Results. In T2DM patients, glucose levels significantly correlated with the fraction of neutrophilic granulocytes, including segmental neutrophils, lymphocytes,

Résumé

Les valeurs diagnostiques de l'hémogramme complet en diabète sucré de type 2 et les comorbidités

Introduction. Le diabète sucré est souvent associé à la pancréatite et le surpoids. Jusqu'à présent, les résultats des tests de routine de laboratoire ne sont pas utilisés en tant que marqueurs surs des comorbidités associées au diabète sucré de type 2 (DT2).
L'objectif de l'étude. Le but de l'étude était d'analyser les paramètres de l'hémogramme complet (la formule sanguine complète) afin de déterminer les prédicteurs significatifs de l'évolution de la comorbidité DT2.
Matériel et méthodes. L'étude portait sur 579 patients atteints de DT2 ayant comme comorbidités le surpoids/l'obésité et la pancréatite chronique. L'hémogramme complet (la formule sanguine complète) a été réalisée à l'aide d'un analyseur d'hématologie automatique Yumizen H 500 CT. Les taux d'insuline ont été déterminés à l'aide d'un Kit standard avec un analyseur d'analyse immuno- enzymatique Thermo scientifique Multiskan FC. Le taux du glucose a été déterminé à l'aide d'un Kit avec un analyseur biochimique

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and NLR, while glycated hemoglobin (HbA1c) levels were significantly correlated with the lymphocyte and NLR fractions. Notably, no correlations between leukocyte profile and carbohydrate metabolism variables were found in T2DM patients. We found a negative correlation between glucose levels and the rod-shaped neutrophilic granulocyte fraction, as well as between HbA1c and NLR levels in overweight T2DM patients without CP. In overweight T2DM patients with comorbid CP, glucose levels correlated with the lymphocyte and NLR fractions.

Conclusion. T2DM in overweight/obese patients with CP is characterized by an abnormal and uncontrolled leukocyte response, therefore a complete blood count is not an adequate marker of the comorbid course of diabetes in such patients.

Keywords: type 2 diabetes mellitus, obesity, chronic pancreatitis, complete blood count.

automatique COBAS INTEGRA DIAGNOSTIC. Le rapport neutrophile- lymphocyte (NLR) a été calculé sur base de l'hémogramme complet.

Résultats. Chez les patients atteints de DT2, les taux de glucose étaient significativement corrélés avec la fraction granulocytes neutrophiles, y compris les neutrophiles segmentaires, les lymphocytes et le NLR, tandis que les taux d'hémoglobine glyquée étaient corrélés avec les fractions de lymphocytes et de NLR. Aucune corrélation entre le profile leucocytaire et les variables du métabolisme des glucides n'a été trouvée chez les patients atteints de DT2. Nous avons trouvé une corrélation négative entre le taux de glucose et la fraction granulocytaire neutrophile en forme de bâtonnet, ainsi qu'entre les taux d'hémoglobine glyquée et du NFL chez les patients présentant une comorbidité de surpoids et de pancréatite chronique. Les taux de glucose étaient corrélés aux fractions lymphocytaires et NLR chez les patients atteints de DT2 ayant comme comorbidités le surpoids et la pancréatite chronique

Conclusion. Le DT2 chez les patients avec surpoids/obésité atteints de pancréatite chronique est caractérisé par une réponse leucocytaire anormale et incontrôlée ainsi que l'hémogramme complet n'est pas un marqueur adéquat de l'évolution comorbide du diabète chez ces patients.

Mots-clés: le diabète sucré de type 2, obésité, pancréatite chronique, hémogramme complet.

Introduction

It is estimated that 415 million adults worldwide, or one person out of 11 in the cohort of people aged 20 to 79 years, suffer from diabetes mellitus (DM)[1]. In 2016, diabetes was the seventh leading cause of death, accounting for 1.6 million deaths[2]. Patients with type 2 diabetes mellitus (T2DM) share risk factors such as obesity, endothelial dysfunction, vascular inflammation and dyslipidaemia[3], and thus have a higher risk of cardiovascular complications[4], kidney disease[5] and hypertension[6]. In addition, patients with DM have a higher risk of depression[7], gastrointestinal tract diseases[8], thyroid gland disorders[9] and chronic obstructive pulmonary disease[10]. DM is closely associated with overweight and low physical activity. Studies indicate that 86% of adults with diabetes are overweight or obese, and of this number, 52% are obese and 8.1% are morbidly obese[11]. A substantial proportion of research literature is focused on the development of diabetes in patients with pancreatitis[12], however, there is also an inverse relationship: exocrine insufficiency of the pancreas is found in 35% of patients with DM[13]. To date, the results of routine clinical tests are not being utilized as reliable markers for comorbidities of T2DM.

The objective of the study

The aim of our study was to analyze complete blood count parameters to determine significant predictors of the comorbid course of T2DM.

Materials and methods

The study involved 579 patients with T2DM, who were admitted to the Endocrinology department of Ternopil University Hospital, Ukraine, between 2018-2019. The patients were placed in study groups according to their comorbidities, and these groups are presented in Table 1.

There were no significant age and sex differences between the patient groups. All patients were informed about the purpose of the study and gave a written consent for participation. The information on patient's identity and health status has remained confidential.

T2DM diagnosis was verified following the guidelines of the American Diabetes Association

Table 1. Study groups (n = 579).

Group	*Patient cohort*	*n*	*%*
1	T2DM patients with normal body weight and without chronic pancreatitis	67	11.57
2	T2DM patients with normal body weight and with concomitant chronic pancreatitis	32	5.53
3	T2DM patients with overweight and without chronic pancreatitis	126	21.76
4	T2DM patients with overweight and with concomitant chronic pancreatitis	33	5.70
5	T2DM patients with obesity and without chronic pancreatitis	262	45.25
6	T2DM patients with obesity and with concomitant chronic pancreatitis	59	10.19

(2019)[14]. Diabetes was diagnosed taking into account the glycated hemoglobin (HbA1c) levels of ≥6.5%, which were determined using an automatic biochemical analyzer COBAS 6000 (Roche Hitachi, Germany).

Chronic pancreatitis (CP) diagnosis was verified using the Unified Clinical Protocol of Primary, Secondary (Specialized) Medical Care and Medical Rehabilitation "Chronic Pancreatitis" and the guidelines of the American Pancreatic Association[15,16].

Body mass index (BMI) was calculated using the following formula: BMI = body weight (kg)/ height (m^2). Data were interpreted according to World Health Organization recommendations: normal weight falls within the range of 20.0 – 24.9 kg/m^2; overweight 25.0-29.9 kg/m^2; Class 1 obesity 30.0-34.9 kg/m^2; Class 2 obesity 35.0-39.9 kg/m^2 and Class 3 obesity > 40 kg/m^2 [17].

Inclusion criteria: clinical, laboratory and instrumental signs of T2DM, CP and obesity, no significantly elevated levels (not more than 3-fold) of bold alpha-amylase, lipase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl-transpeptidase.

Exclusion criteria: clinically significant signs of neurological, mental, renal, hepatic, immunological, gastrointestinal, urogenital disorders; injury of the musculoskeletal system, skin, sensory organs, the endocrine system (except T2DM); un-managed hematological diseases; acute pancreatitis, not stabilized or life-threatening heart disease. We also excluded patients with malignant neoplasms who have not been in complete remission for at least 5 years, and those with drug and alcohol dependence.

Complete blood count (CBC) was performed using a Yumizen H500 CT automatic hematology analyzer. Insulin levels in blood serum were determined using a Thermo Scientific Multiskan FC enzyme-linked immunoassay analyzer. Glucose levels in blood serum were determined using a standard kit with a COBAS INTEGRA® Diagnostics automatic biochemical analyzer. The neutrophil-to-lymphocyte ratio (NLR) was calculated dividing neutrophils by lymphocytes.

Statistical analysis of the results was performed using the STATISTICA 7.0 software. Statistical analysis methods were selected considering the normality of population distribution for the studied variables.

Given the absence of underlying distribution in quantitative variables, we calculated the median (Me), lower (Lq) and upper (Uq) quartiles for the purposes of descriptive statistical analysis.

Comparative analysis of quantitative variables in three or more groups was performed using the Kruskal–Wallis one-way analysis of variance, which was considered statistically significant at $p<0.05$. Further pairwise comparison of groups was performed using the Mann-Whitney U-test, with Bonferroni correction for assessing the level of statistical significance.

Results

We observed no pathological changes in the red blood cells counts in patients of all experimental groups. Using the Kruskal–Wallis test by ranks, leukocyte counts in the blood of patients from different experimental groups showed significant differences (Table 2).

There was a significant difference in leukocyte counts (LC) in the blood of patients between Groups 1 and 4 as well as 2 and 4. Groups of patients with co-morbidities had lower LCs compared to Group 1, with the lowest LC detected in the Group 6, the patients with T2DM comorbid with overweight and CP (Table 3).

A survey of carbohydrate metabolism indices in the T2DM patients of different groups revealed a significant difference in the HbA1c levels when analyzed with Kruskal–Wallis test by ranks (Table 4). HbA1c levels were significantly different between Groups 2 and 3 ($p = 0.021$); 2 and 5 ($p = 0.003$); as well 2 and 6 ($p = 0.008$). The highest HbA1c level was detected in the patients of Group 4, with T2DM comorbid with CP.

In the T2DM patients of all Groups, glucose levels significantly correlated with the fraction of neutrophilic granulocytes, including segmented neutrophils,

Table 2. Leukocyte composition in patients with comorbid T2DM.

Groups	*Leukocytes, ×10⁹/L*	*Banded neutrophils, %*	*Segmented neutrophils, %*	*Neutrophilic granulocytes, %*	*Eosinophils, %*	*Basophils, %*	*Monocytes, %*	*Lymphocytes, %*	*Neutrophils / lymphocytes ratio (NLR)*
Group 1	6.76 (6.10; 8.20)	4 (3; 7)	62 (53; 65)	66 (57; 70)	1 (1; 3)	1 (1; 1)	3 (1; 5)	30 (23; 36)	2.16 (1.66; 3.13)
Group 2	6.95 (5.55; 9.00)	5 (3; 8)	62 (52; 67)	70 (55; 74)	1 (1; 3)	0 (0; 0)	2 (1; 4)	27 (25; 39)	2.54 (1.45; 2.84)
Group 3	6.10 (4.90; 7.84)	4 (3; 6)	59 (53; 64)	63 (55; 69)	2 (1; 3)	1 (1; 1)	4 (2; 5)	32 (25; 38)	1.98 (1.50; 2.81)
Group 4	5.30 (4.60; 6,50)	4 (2; 6)	55 (50; 61)	58 (54; 64)	1 (1; 2)	1 (0; 1)	4 (1; 6)	36 (28; 41)	1.57 (1.35; 2.29)
Group 5	6.10 (5.10; 7.20)	5 (3; 6)	59 (51; 63)	63 (56; 69)	2 (1; 3)	1 (1; 1)	3 (2; 5)	31 (25; 38)	2.06 (1.54; 2.67)
Group 6	6.13 (5.40; 7.70)	5 (3; 7)	57 (51; 63)	63 (57; 68)	2 (1; 3)	1 (1; 1)	3 (1; 5)	32 (26; 39)	2.00 (1.44; 2.54)
Kruskal–Wallis H	H=21.32; p<0.001*	H=3.40; p=0.639	H=7.97; p=0.158	H=6.59; p=0.253	H=0.85; p=0.974	H=0.72; p=0.982	H=3.05; p=0.693	H=7.19; p=0.207	H=6.94; p=0.225

Note: * – significant difference

Table 3. Probability values (p) of a test for differences in LC among the Groups.

	Group 1	*Group 2*	*Group 3*	*Group 4*	*Group 5*	*Group 6*
Group 1		1.000	0.434	**0.001***	0.077	1.000
Group 2	1.000		0.753	**0.005***	0.276	1.000
Group 3	0.434	0.753		0.164	1.000	1.000
Group 4	**0.001***	**0.005***	0,164		0.231	0.134
Group 5	0.077	0.276	1.000	0.231		1.000
Group 6	1.000	1.000	1.000	0.134	1.000	

Note: * – significant difference

Table 4. Indices of carbohydrate metabolism in the different groups of patients with T2DM

Groups	*Glucose, mmol/L*	*Insulin, mIU/mL*	*HbA1c, %*
Group 1	10.85 (7.90; 13.74)	9.51 (6.27; 11.90)	8.55 (7.20; 10.30)
Group 2	11.11 (8.08; 18.10)	7.33 (4.85; 8.19)	9.80 (8.47; 11.80)
Group 3	9.21 (7.92; 13.24)	6.77 (3.12; 8.00)	8.40 (7.50; 9.90)
Group 4	11.24 (7.45; 14.51)	8.32 (4.41; 11.90)	9.30 (8.05; 10.57)
Group 5	8.88 (6.72; 12.16)	6.74 (4.77; 13.40)	8.43 (7.20; 9.70)
Group 6	9.93 (8.25; 13.69)	19.07 (7.28; 20.10)	8.30 (7.30; 9.50)
Kruskal–Wallis H	H=9.51; p=0.090	H=4.86; p=0.433	H=20.83; p<0.001*

Note: * – significant difference

Table 5. Correlation between leukocyte profile and carbohydrate metabolism variables in T2DM patients regardless of the presence of comorbid pathology (n = 579)

Variables	*Glucose, mmol/L*	*Insulin, mIU/mL*	*HbA1c, %*
Leukocytes, ×10⁹/L	r=0.04; p=0.498	r=0.18; p=0.145	r=0.04; p=0.343
Banded neutrophils, %	r=(-0.05); p=0.431	r=0.13; p=0.324	r=0.02; p=0.598
Segmented neutrophils, %	**r=(-0.17); p=0.010***	r=0.11; p=0.384	r=-0.09; p=0.056
Neutrophilic granulocytes, %	**r=(-0.18); p=0.007***	r=0.15; p=0.247	r=(-0.07); p=0.132
Eosinophils, %	r=0.11; p=0.138	r=(-0.06); 0.713	r=0.03; p=0.578
Basophils, %	r=(-0.19); p=0.373	r=(-0.40); p=0.373	r=0.21; p=0.182
Lymphocytes, %	**r=0.17; p=0.008***	r=(-0.15); p=0.230	**r=0.10; p=0.022***
Monocytes, %	r=0.04; p=0.559	r=(-0.01); p=0.946	r=(-0.05); p=0.269
Neutrophils / lymphocytes ratio (NLR)	**r=(-0.19); p=0.004***	r=0.17; p=0.176	**r=(-0.09); p=0.041***

Note 1: r – correlation coefficient; p – p-value.
Note 2: * – significant difference

Table 6. Correlation between leukocyte profile and carbohydrate metabolism variables in overweight T2DM patients without CP (n = 126)

Variables	*Glucose, mmol/L*	*Insulin, mIU/mL*	*HbA1c, %*
Leukocytes, $\times 10^9$/L	r=0.11; p=0.414	r=0.16; p=0.578	r=0.07; p=0.476
Banded neutrophils, %	**r=(-0.33); p=0.019***	r=0.30; p=0.301	r=(-0.13); p=0.193
Segmented neutrophils, %	r=(-0.18); p=0.217	r=0.21; p=0.475	r=(-0.15); p=0.124
Neutrophilic granulocytes, %	r=(-0.16); p=0.257	r=0.26; p=0.365	r=(-0.16); p=0.091
Eosinophils, %	r=0.24; p=0.161	r=0.16; p=0.614	r=(-0.05); p=0.660
Basophils, %	r=(-0.14); p=0.725	–	r=0.38; p=0.161
Lymphocytes, %	r=0.21; p=0.150	r=(-0.22); p=0.457	r=0.19; p=0.054
Monocytes, %	r=(-0.05); p=0.734	r=0.18; p=0.548	r=(-0.14); p=0.164
Neutrophils / lymphocytes ratio (NLR)	r=(-0.24); p=0.102	r=-0.24; p=0.418	**r=(-0.19); p=0.047***

Note 1: r – correlation coefficient; p – p-value.
Note 2: * – significant difference

Table 7. Correlation between leukocyte profile and carbohydrate metabolism variables in the overweight patients with T2DM comorbid with CP (n = 33)

Variables	*Glucose, mmol/L*	*Insulin, mIU/mL*	*HbA1c, %*
Leukocytes, $\times 10^9$/L	r=0.26; p=0.377	r=(-0.50); p=0.667	r=0.09; p=0.628
Banded neutrophils, %	r=0.28; p=0.380	r=(-0.87); p=0.333	r=0.19; p=0.374
Segmented neutrophils, %	r=(-0.55); p=0.054	–	r=0.16; p=0.441
Neutrophilic granulocytes, %	r=(-0.64); p=0.018	–	r=0.24; p=0.245
Eosinophils, %	r=(-0.24); p=0.539	r=(-0.87); p=0.333	r=0.12; p=0.593
Basophils, %	–	–	r=(-0.87); p=0.333
Lymphocytes, %	**r=0.59; p=0.034***	r=(-0.50); p=0.667	r=(-0.21); p=0.294
Monocytes, %	r=0.26; p=0.384	–	r=(-0.05); p=0.830
Neutrophils / lymphocytes ratio (NLR)	**r=(–0.65); p=0.017***	r=0.50; p=0.667	r=0.24; p=0.230

Note 1: r – correlation coefficient; p – p-value.
Note 2: * – significant difference

lymphocytes, and NLR, while HbA1c levels were significantly correlated with the lymphocyte and NLR fractions (Table 5). Notably, no correlations between leukocyte profile and carbohydrate metabolism variables were found in the T2DM patients with normal body weight and no CP (Group 1), normal weight T2DM patients with comorbid CP (Group 2), T2DM and obesity without CP (Group 5) and in T2DM overweight patients with comorbid CP (Group 6).

We found a negative correlation between glucose levels and the banded neutrophilic granulocyte fraction, as well as between HbA1c and NLR levels in overweight T2DM patients without CP (Table 6).

In overweight patients with T2DM and comorbid CP, glucose levels correlated with the lymphocyte and NLR fractions (Table 7).

Discussion

Obesity is a key factor in the development and progression of T2DM, as well as its complications[18-20]. Abdominal fat stimulates fat cells to secrete pro-inflammatory substances, resulting in the development of insulin resistance, the main trigger of DM[21,22]. At the same time, obesity is a recognized risk factor for pancreatic diseases, including CP. The main mechanisms involved are the increased inflammation and necrosis caused by the build-up in intra- and peripancreatic fat[23]. Triacylglycerols account for more than 80% of the adipocyte weight, and its hydrolysis by lipases produces free fatty acids, which are implicated in the induced death of pancreatic cells[24]. Moreover, this type of cell death also involves interleukins (IL) – IL1β and IL8[25]. Although inflammation is one of the pathogenic components of T2DM, CP and obesity, in this study the recognized indicators of the inflammatory process, such as leukocyte count and leukocyte profile fractions, were within the physiological range[26], a finding that was consistent with other studies[27]. Previous studies showed that chronic inflammatory diseases are characterized by an abnormal and uncontrolled leukocyte response[28]. It is remarkable that in this study the lowest absolute number of leukocytes was found in overweight patients with T2DM and CP. This variable was also significantly lower when compared to patients with T2DM only and patients with comorbid T2DM and CP, which suggests that overweight, but not obesity, plays a role in the changes in white blood cell count. The current research links the increase in fat to the increase in white blood cells indicating inflammation[29,30]. Ryder et al. showed that higher white blood cell counts in obese patients are associated with insulin resistance[31], while Twig et al. argued that a normal leukocyte count relatively protected overweight and obese men from developing T2DM compared

to overweight or obese individuals with high white blood cell counts[32]. However, our study found the lowest leukocyte count value in overweight patients who already had T2DM and CP. If we consider overweight as the main factor affecting the level of leukocytes in this patients' cohort, we can infer that such a low value might be the consequence of a weight loss diet per standard disease management protocol. The mechanism involved in the association between weight loss and WBC reduction is not fully understood, but is likely connected to leptin exposure[33].

The high level of HbA1c observed in the comorbid course of T2DM and CP is likely due to the close relationship between high glucose levels and inflammation, which was increased in patients with CP[34]. Our study also showed a negative association between HbA1c and NLR levels in overweight diabetic patients. Sefil et al. found a positive correlation of NLR with HbA1c, but not with body mass index[35]. Other studies showed that elevated NLR levels are associated with higher levels of various pro-inflammatory cytokines[36], which can cause cellular DNA damage. On the other hand, the increase in cytokines under inflammation causes lymphopenia[37] and neutrophilia[38], subsequently increasing NLR, while in our study the level of lymphocytes directly correlated with fasting glucose levels. Fang et al. did not find a correlation between NLR and obesity or metabolic syndrome, suggesting a low diagnostic value of NLR in these conditions, possibly because neutrophils and lymphocytes increased in parallel with the severity of obesity and metabolic syndrome, negating a potential NLR increase[39]. It is also worth mentioning the "obesity paradox" described by JP Wilding: patients with normal body weight at the time of T2D diagnosis had a higher risk of developing cardiovascular complications, in contrast to overweight individuals with T2DM[40]. These results suggest that the role of overweight is not yet clearly defined and give grounds to consider overweight as a factor of protection or compensation in the comorbid course of T2DM and CP, requiring a more detailed study.

Conclusions

T2DM comorbid with overweight/obesity and CP is characterized by an abnormal and uncontrolled leukocyte response, therefore a complete blood count is not an adequate marker of the comorbid course of diabetes in such patients.

Author Contributions:

Conceptualization, M.M.; methodology, U.H; software, K.K; validation, U.H; formal analysis, U.H.; investigation, U.H; resources, I.K.; data curation, U.H.; writing–original draft preparation, U.H. and K.K.; writing–review and editing, I.K. and M.M.; visualization, I.K.; supervision, M.M. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The ethical principles included in the Declaration of Human Rights adopted in Helsinki, in 1975, and revised in 2008, were fully respected in our study. The enrolled subjects participated in this study voluntarily, completed and signed a written informed consent. Study protocol was approved by the Ethics Committee of I. Horbachevsky Ternopil National Medical University"

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