

## The effects of anti-diabetic agents on white blood cells

AbdulRahman J Manssor<sup>1</sup>, Hassan Kh Rajab<sup>2</sup>

<sup>1</sup> Department of Physiology, College of Medicine, University of Tikrit, Tikrit, Iraq

<sup>2</sup> Department of Pharmacology, College of Medicine, University of Tikrit, Tikrit, Iraq

(Received: 16 / 3/ 2010 ---- Accepted: 13 / 12 / 2010)

### Abstract:-

A 105 diabetic patients included in this study . the patients groups according to their type of therapy into four groups the first group include 25 patients on insulin therapy ,the second group include 29 patients on sulfonylurea (oral hypoglycemic agent- glibenclamide-5mg). The third group include 24 patients on sulfonylurea & insulin & the fourth group include 27 patients on sulfonylurea & metformin (Biguanides) . Blood sample was taken to estimate both hemoglobin concentration & white blood cell count .The hemoglobin results in the first group only 10 patients with normal result , 13 patients with mild anemic results & two patients with moderate results .In the second group only 12 patients with normal result &17 patients with mild anemic results. In the third group only 11 patients with normal result , 12 patients with mild anemic results & one patient with moderate results .In the fourth group only 8 patients with normal result , 16 patients with mild anemic results & three patients with moderate results . The white blood cell count obtain in this study among the four groups was in the first group one out of 25(4%) patients give result below normal . In the second group seven out of 29(24.1%) give results below normal . In the third group four out of 24(16.7%)patients give result below normal . In the fourth group five out of 27.( 18.5%) patients give results below normal . No significant differences see regarding age, sex , duration of disease , duration of therapy , types of therapy & if take sulfonylurea alone or in combination . Although a high percentage of leukopenia in those on sulfonylurea .

### Introduction

#### White blood cell

White blood cells (WBCs), or leukocytes (also spelled "leucocytes"), are cells of the immune system defending the body against both infectious disease and foreign materials. Five<sup>[1]</sup> different and diverse types of leukocytes exist, but they are all produced and derived from a multipotent cell in the bone marrow known as a hematopoietic stem cell. Leukocytes are found throughout the body, including the blood and lymphatic system.<sup>[2]</sup> The number of WBCs in the blood is often an indicator of disease. There are normally between  $4 \times 10^9$  and  $11 \times 10^9$  white blood cells in a litre of blood, making up approximately 1% of blood in a healthy adult.<sup>[3]</sup> An increase in the number of leukocytes over the upper limits is called leukocytosis, and a decrease below the lower limit is called leukopenia. The physical properties of leukocytes, such as volume, conductivity, and granularity, may change due to activation, the presence of immature cells, or the presence of malignant leukocytes in leukemia.<sup>[4]</sup>

#### Etymology:

The name "white blood cell" derives from the fact that after centrifugation of a blood sample, the white cells are found in the buffy coat, a thin, typically white layer of nucleated cells between the sedimented red blood cells and the blood plasma.<sup>[5]</sup> The scientific term *leukocyte* directly reflects this description, derived from Greek *leukos* (white), and *kytos* (cell). Blood plasma may sometimes be green if there are large amounts of neutrophils in the sample, due to the heme-containing enzyme.<sup>[6]</sup>

#### Medication causing leukopenia:

Some medications can have an impact on the number and function of white blood cells. Leukopenia is the reduction in the number of white blood cells, which may affect the overall white cell count or one of the specific populations of white blood cells. For

example, if the number of neutrophils is low, the condition is known as neutropenia. Likewise, low lymphocyte levels are termed lymphopenia.<sup>[7]</sup> Medications which can cause leukopenia include clozapine, an antipsychotic medication with a rare adverse effect leading to the total absence of all granulocytes (neutrophils, basophils, eosinophils).<sup>[8]</sup> Other medications include immunosuppressive drugs, such as sirolimus, mycophenolate mofetil, tacrolimus, and cyclosporine. Interferons used to treat multiple sclerosis, like Rebif, Avonex, and Betaseron, can also cause leukopenia. Oral hypoglycemic agents also can cause leukopenia .<sup>[9]</sup>

#### Fixed leukocytes:

Some leukocytes migrate into the tissues of the body to take up a permanent residence at that location rather than remaining in the blood. Often these cells have specific names depending upon which tissue they settle in, such as fixed macrophages in the liver which become known as Kupffer cells. These cells still serve a role in the immune system.<sup>[10]</sup>

#### The aim of study to estimate white blood cells counts in diabetic patients on different types of therapy

#### Patients & methods:

This study carried out at July 2009-January 2010 in Tikrit city . A 105 diabetic patients included in this study . the patients groups according to their type of therapy into four groups . The first group include 25 patients on insulin therapy . The second group include 29patients on sulfonylurea(oral hypoglycemic agent- glibenclamide-5mg ). The third group include 24 patients on sulfonylurea & insulin . the fourth group include 27 patient on sulfonylurea & metformin(Biguanides ) as showed in table -1-. A questioner was perform including age , six , duration of diabetes disease , drinking ,smoking , history of previous blood disorders , familial history of diabetes

disease . Blood sample was taken to estimate both hemoglobin by microhematocrit reader use centrifuge (Micro)Hematocrit tube & white blood cell count Total WBC count : Diluting method Aspirate EDTA blood to 0.5 mark of WBC diluting pipette, wipe outside with soft paper.

- Aspirate Turk's solution to 11 mark
- Mix horizontally with pipette shaker
- Fill hemacytometer or counting chamber
- Count WBC in the "ruled area (W)" area on each side of counting chamber by 10x objective lens and strictly follow the "boundary rule"
- Count both sides (1,2) & measure blood sugar levels simply and quickly with a home blood glucose level testing kit. All kits have at least two things: a measuring device and a strip. All data were presented as a mean and standard deviation (S.D) & t- test. Statistically significant

### Results :

The patients age range 15-63 years (average  $25.6 \pm 3$ ) while their sex as follow male 46 patients & female 59 patients table-2- showed both age & sex distribution among diabetic patients. Table-3- showed patients profile as follow: smoking 31 patients, drinking 3 , duration of diabetic disease 4-15 years , positive familial disease 51 patients , history of blood disorder were nil .The hemoglobin results showed in table -4- in the first group only 10 patient with

normal result , 13 patients with mild anemic results & two patients with moderate results .In the second group only 12 patient with normal result & 17 patients with mild anemic results. In the third group only 11 patient with normal result , 12 patients with mild anemic results & one patient with moderate results .In the fourth group only 8 patient with normal result , 16 patients with mild anemic results & three patients with moderate results . The white blood cell count obtain in this study among the four groups as showed in table -5- in the first group one out of 25(4%) patients give result below normal. In the second group five out of 29(17.24%) give results below normal. In the third group two out of 24(8.3%) patients give result below normal. In the fourth group three out of 27(11.1%) patients give results below normal. Table-6- showed patients profile who developed leukopenis as follow 7 out of 46 male to 10 out of 59 female, 5 out of 37 in those with duration of disease below 10 years to 12 out of 68 in those above 10 years, 13 out of 86 in those aged below 50 years to 4 out of 19 in those above 50 years old , 16 out of 80 in those included sulfonylurea in their treatment to 1 out of 25 not used sulfonylurea & 7 out of 29 used sulfonylurea as alone to 9 out of 51 used combine therapy of sulfonylurea plus other agents & another table showed patients profile, Hb distribution & classification according type of therapy.

**Table-1- classification of patients according to their type of therapy**

| Group           | Number | The type of therapy   |
|-----------------|--------|---|
| 1 <sup>st</sup> | 25     | On insulin therapy only   |
| 2 <sup>nd</sup> | 29     | On glibenclamide (a sulfonylurea -oral hypoglycemic agent)          |
| 3 <sup>rd</sup> | 24     | On insulin+ glibenclamide (oral hypoglycemic agent)                 |
| 4 <sup>th</sup> | 27     | On glibenclamide + metformin (a biquanide -oral hypoglycemic agent) |

**Table-2- age & sex distribution among the patients**

| Age range          | Number | Sex        |            |
|--------------------|--------|------------|------------|
|                    |        | Male       | Female     |
| Less than 20 years | 27     | 11 = 40.7% | 16 = 59.3% |
| 20-29 years        | 29     | 17 = 58.6% | 12 = 41.4% |
| 30-39 years        | 10     | 4 = 40%    | 6 = 60%    |
| 40-49 years        | 20     | 8 = 40%    | 12 = 60%   |
| Above 50 years     | 19     | 6 = 31.6%  | 13 = 68.4% |
| Total              | 105    | 46 = 43.8% | 59 = 56.2% |

**Table-3-patients profile**

| Character                                | Number     |
|--|------------|
| Smoking                                  | 31 = 29.5% |
| drinking                                 | 3 = 2.9%   |
| Positive familial history of the disease | 51 = 48.8% |
| History of blood disorder                | Nil        |
| Duration of the disease                  | 4-14 years |

Table-4-the hemoglobin distribution among patients groups

| Groups          | Number | Normal <sup>[11]</sup> * | Abnormal   |           |
|-----------------|--------|--------------------------|------------|-----------|
|                 |        |                          | Mild       | Moderate  |
| 1 <sup>st</sup> | 25     | 10 = 40%                 | 13 = 52%   | 2 = 8%    |
| 2 <sup>nd</sup> | 29     | 12 = 41.4%               | 17 = 58.6% | --        |
| 3 <sup>rd</sup> | 24     | 11 = 45.8%               | 12 = 50%   | 1 = 4.2%  |
| 4 <sup>th</sup> | 27     | 8 = 29.6%                | 16 = 59.3% | 3 = 11.1% |
| Total           | 105    | 41 = 39.1%               | 58 = 55.2% | 6 = 5.7%  |

\* normal level in male & in female

Table-5-white blood cells counts according to the patients groups

| Group           | Number | Normal count <sup>[11]</sup> 4-11x10 <sup>9</sup> | Below 4-11x10 <sup>9</sup> |
|-----------------|--------|---|----------------------------|
| 1 <sup>st</sup> | 25     | 24 = 96%  | 1 = 4%                     |
| 2 <sup>nd</sup> | 29     | 22 = 75.9 %                                       | 7 = 24.1%                  |
| 3 <sup>rd</sup> | 24     | 20 = 83.3%  | 4 = 16.7%                  |
| 4 <sup>th</sup> | 27     | 22 = 81.5 %                                       | 5 = 18.5%                  |
| Total           | 105    | 88 = 83.8%  | 17 = 16.2%                 |

Table-6- profile of patients develop leukopenia

| Character                    | Sub-character              | Patients number | Normal value | Number developed leukopenia | Chi square test $\chi^2$ |
|------------------------------|----------------------------|-----------------|--------------|-----------------------------|--------------------------|
| sex                          | Male                       | 46              | 39           | 7                           | N.S                      |
|                              | Female                     | 59              | 49           | 10                          |                          |
| Duration of diabetic disease | Below 10 years             | 37              | 32           | 5                           | N.S                      |
|                              | Above 10 years             | 68              | 56           | 12                          |                          |
| Patient's age                | Below 50 years             | 86              | 73           | 13                          | N.S                      |
|                              | Above 50 years             | 19              | 15           | 4                           |                          |
| Therapy type                 | Included sulfonylurea      | 80              | 64           | 16                          | N.S                      |
|                              | Not include d sulfonylurea | 25              | 24           | 1                           |                          |
| Sulfonylurea                 | Used sulfonylurea alone    | 29              | 22           | 7                           | N.S                      |
|                              | Used combine therapy       | 51              | 42           | 9                           |                          |
| Anemia                       | Patients used sulfonylurea | 25              | 15           | 10                          | N.S                      |
|                              | Patients not used it       | 80              | 49           | 31                          |                          |

N.S= not significant at 1% & 5%

### Discussion :-

In this study different therapy models were included to investigate the extend of different agents used in treatment of diabetes patients. As showed in table -6- there is no significant differences between those used & those not used sulfonylurea agent although many studies & textbok indicate the causing of sulfonylurea a leukopenic effects , however of the fact that a high percentage of patients developed leukopenis in those used sulfonylurea to those not used <sup>[10-18]</sup> . According to patient age if it is affecting the obtained result or not, table -6- showed no significant differences between age group and there is no any indicator that patient's age affecting the incidence of leukopenia effect on using sulfonylurea <sup>[13,15,16]</sup> . The duration of exposure to the anti -diabetic agents were also included in this study to see if there is any differences in developing of leukopenic effects

obtain due to more chronically of using the anti-diabetic agents or not , no significant differences seen due to enlongation or shortening the period of exposure to the sulfonylurea therapy since two cases reported that develop leukopenia after 5 years of sulfonylurea therapy. There is no significant differences between the sex in developing leukopenia as showed in table -6-. The using of sulfonylurea alone or in combination not affecting the incidence of leukopenia as showed in table -6- in spite of a high percentage of developing leukopenis in those used it alone to those used in combination , but the fact that non of the combine agent decrease the possibility of developing leukopenia <sup>[12-14, 19]</sup> . The anemia developed cantnot related it to the using of sulfonylurea since there is no significant differences between those used it and those not used it as showed in table -6- although sulfonylurea induce itself anemia <sup>[10,13]</sup> .

**Reference:-**

- 1-LaFleur-Brooks, M. (2008). *Exploring Medical Language: A Student-Directed Approach, 7th Edition*. St. Louis, Missouri, USA: Mosby Elsevier. pp. 398. [ISBN 978-0-323-04950-4](#).
- 2-Maton, D., Hopkins, J., McLaughlin, Ch. W., Johnson, S., Warner, M. Q., LaHart, D., & Wright, J. D.(1000008). *Human Biology and Health*. Englewood Cliffs, New Jersey, USA: Prentice Hall. [ISBN 0-13-981176-1](#).
- 3-Alberts, B. (2005). "Leukocyte functions and percentage breakdown". *Molecular Biology of the Cell*. NCBI Bookshelf. <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=leukocyte,functions&rid=mboc4.table.4143>. Retrieved 2007-04-14.
- 4-Gartner, L. P., & Hiatt, J. L. (2007). *Color Textbook of Histology* (3rd ed.). Philadelphia, PA: SAUNDERS Elsevier. pp. 225.
- 5- Daniels, V. G., Wheeler, P. R., & Burkitt, H. G. (1979). *Functional histology: A text and colour atlas*. Edinburgh: Churchill Livingstone. [ISBN 0-443-01657-7](#).
- 6-Semester 4 medical lectures at Uppsala University 2008 by Leif Jansson
- 7-Krombach, F., Münzing, S., Allmeling, A. M., Gerlach, J. T., Behr, J., & Dörger, M. (1 September 1997). "Cell size of alveolar macrophages: an interspecies comparison". *Environ. Health Perspect.* 105 Suppl 5: 1261–3. [doi:10.2307/3433544](#). [ISSN 00916765](#). [PMID 9400735](#).
- 8-Pantaleo, G., Demarest, J. F., Soudeyns, H., *et. al.* (August 1994). "Major expansion of CD8+ T cells with a predominant V beta usage during the primary immune response to HIV". *Nature* 370 (6489): 463–7. [doi:10.1038/370463a0](#). [PMID 8047166](#).
- 9- Hulin et al., "The Glitazone Family. ", *Current Pharm. Design*. 1996, vol. 2, No. 1, pp. 85-.
- 10- Richard Finkel et al. Lippincotts illustrated reviews: pharmacology. Insulin and oral hypoglycemic drugs. LIPPINCOTT WILLIAM & wilkins. 2009. 23pp(285-298) .
- 11- AHFS Drug Information. (CR) Copyright, 1959-2009, Selected Revisions January 2008. American Society of Health-System Pharmacists, Inc., 7272 Wisconsin Avenue, Bethesda, Maryland 20814
- 11-William F.Ganong. Review of medical physiology (12<sup>th</sup> ed). Circulating body fluids . McGraw-Hill Companies.2001; 12<sup>th</sup> ed , 27, pp500-510.
- 12- Oakes et al., "A New Antidiabetic Agent . . . ", *Diabetes* vol. 43, 1994 p. 1203.
- 13- Groop et al., "Sulfonylureas in NIDDM", *Diabetes Care*, 1992, vol. 15, No. 6, pp. 737-754.
- 15- Nakano et al., CS-045, "Clinical Evaluation . . . ", *English Transl. No. 138-007*, pp. 1-38 (1993).
- 16- Henry L. Wildberger, M.D.; Henry T. Ricketts, M.D. *J Am Med Assoc* effects of sulfonylurea drugs in hospitalized diabetic patients. 1996;162(11): 1045-1049
- 17- Vanessa J Briscoe<sup>1</sup> *PhD*, Michelle L Griffith<sup>1</sup> *MD* & Stephen N Davis. *MD* . The role of glimepiride in the treatment of type 2 diabetes mellitus. February 2010, Vol. 6, No. 2, Pages 225-235 ,
- 18- Vidushi Sood, Kathleen Colleran, Mark R. Burge. *Diabetes Technology & Therapeutics*. October 2000, 2(3): 429-440.
- 19- Mozghan Dorkhan, Magnus Dencker, Martin Stagmo and Leif Groop. Effect of pioglitazone versus insulin glargine on cardiac size, function, and measures of fluid retention in patients with type 2 diabetes. *Cardiovascular Diabetology* 2009, 8:15 [doi: 10.1186/1475-2840-8-15](#).

## تأثير مضادات السكر على كريات الدم البيضاء

عبد الرحمن جهاد منصور<sup>١</sup> ، حسن رجب شعبان<sup>٢</sup>

<sup>١</sup> فرع الفلسفة ، كلية الطب ، جامعة تكريت ، تكريت ، العراق

<sup>٢</sup> فرع الادوية ، كلية الطب ، جامعة تكريت ، تكريت ، العراق

( تاريخ الاستلام: ١٦ / ٣ / ٢٠١٠ ---- تاريخ القبول: ١٣ / ١٢ / ٢٠١٠ )

### الملخص

مائة و خمسة مريضاً من مرضى داء السكري تَضمَّنوا في هذا الدراسة. قسم المرضى الى مجموعات طبقاً لنوعية العلاج إلى أربع مجموعات المجموعة الأولى ٢٥ مريض يستخدمون علاج انسولين والمجموعة الثانية عددهم ٢٩ مريض يستخدمون حبوب السكر داثونيل ٥ملغم والمجموعة الثالثة عددهم ٢٤ مريض يستخدمون حب داثونيل مع الانسولين اما المجموعة الرابعة عددهم ٢٧ مريض يستخدمون حب داثونيل ٥ملغم مع حب متفورمين. عينة من الدم أُخذت لتُخمين كلا من hemoglobin وإحصاء كريات الدم البيضاء. فيما يخص فحص ال hemoglobin كانت النتيجة كالآتي عشرة مريضى نتيجتهم طبيعية والباقي مصابون بفقر الدم ضمن المجموعة الاولى. اثنا عشرة مريضاً نتيجتهم طبيعية والباقي مصابون بفقر الدم ضمن المجموعة الثانية. احد عشرة مريضاً نتيجتهم طبيعية والباقي مصابون بفقر الدم ضمن المجموعة الثالثة. ثمانية مريضى نتيجتهم طبيعية و الباقي مصابون بفقر الدم ضمن المجموعة الرابعة. اما بالنسبة لعدد كريات الدم البيضاء فان اعداد المرضى المصابين بنقص كريات الدم البيضاء حسب المجموعات كالآتي مريض واحد من مجموع خمس وعشرون مريضاً ضمن المجموعة الاولى وسبعة مريضى من مجموع تسع وعشرون مريضاً ضمن المجموعة الثانية واربعه من مجموع اربع و عشرون ضمن المجموعة الثالثة و خمسة من مجموع سبع و عشرون ضمن المجموعة الرابعة. لا توجد فروقات معنوية هامة فيما يخص العُمَر والجنس ومدة المرض ومدة العلاج و نوع العلاج وإذاما استخدم sulfonyleurea لوحده أو مع انواع اخرى. بالرغم من وجود نسبة عالية من المرضى المصابين بنقص كريات الدم البيضاء leukopenia عند المتناولين sulfonyleurea.