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The Contribution of Interleukin (17) in Iraqi Patients with Type I Diabetic and Positive Agglutination Sera with *Morganella Morganii* Antigens

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ABSTRACT

Background: The rising population of patients with diabetes type 1 has caused in a fast increase in the amount of patients who have diabetic complications. Objective: Isolation of bacteria from diabetic patients and detection of their antibodies in the serum of patients and rabbits. Materials and Methods: Sixty samples of blood and urine were collected from diabetic patients, a similar proportion of genders were included in 50 samples of blood from healthy as controls. Patients with diabetes diseases diagnosed by a physician collected from specialized center for endocrinology and diabetes and Kindy hospital, in Baghdad. Results: This study showed that *Morganella morganii* (n=9, 18%) was isolated from urine of patients. With *M. morganii* antigens (complete cells) as three bacteria antigens agglutinated in titer 1:64 and three in titer 1:128 of serum of patients (antibodies) whereas 1 and fife of *M. morganii* antigens agglutinated in serum of patients in titer 1:256 and 1:16 Consecutively. Determination of the concentration of cytokinetic proteins IL-17, using an ELISA device. The concentration of some inflammation-initiating cytokines was estimated in the serum of the studied samples, which included using IL-17 ELISA technology. The statistical results by t-test showed were significant differences between this interleukin between the patients and the control sample and under the probability level $P<0.05$ in the serum of the patients compared to the control sample. The results also showed a decrease in the cytokinetic concentration, as the concentration in the infected serum was 0.011 ± 0.019 (pg/mm), while its concentration in the control sample was 0.007 ± 0.033 (pg/mm) in the infected serum. Recognize the agglutination ability slide agglutination exam (anti *Morganella morganii* rabbit serum). Conclusion: The ability of killed antigen bacteria isolated from diabetic patients to agglutinate with their serum, and its ability to agglutinate with the serum of rabbits injected with this bacterium. The increased prevalence of agglutination and increased antibodies of patients and rabbit blood suggest this as part of the multifactorial basis for disease penetrance and susceptibility.

1. INTRODUCTION

Diabetes is a disorder; coming about because of both hereditary inclination and preferring ecological factors [1]. Diabetes besets more than 135 million individuals overall, and at regular intervals an American dies of the infection [2]. Diabetes is distinct as a cluster of metabolic diseases categorized by hyperglycemia because of flaws in insulin excretion, insulin act, or a mixture of the two [3]. Kinds of diabetes: There are two different types of diabetes, named type I and type II [4]. Type 1 diabetes is an auto-immune disease ambitious by T cell-intervened devastation insulin-discharging β-cells of the pancreatic islets that frequently shows throughout adolescence [5, 6]. Interleukin-17A (IL-17A), also commonly called IL-17, is produced by the T helper 17 (Th17) subset of CD4+ T cells. The discovery of Th17 cells has been one of the most important advances in T cell immunology since the discovery of Th1 and Th2 cells by Mosmann, Coffman, and their colleagues more than two decades ago [7]. Brodalumab is a human anti-IL17RA monoclonal antibody. It inhibits the activity of 17A/F and 17E. There are several factors targeting the IL-17-TH17 pathway currently under investigation [8]. Th17 cells are known to play an important role in inflammatory and autoimmune diseases [9]. *M. morganii* is widely distributed in the environment and intestines of humans, mammals and reptiles as part of the natural flora. *M. morganii* is very resistant to antibiotics in recent years, and this resistance is carried out through genetic and motile elements. In general, *M. morganii* can produce virulence factors, such as urease, hemolysin, and lipopolysaccharide (LPS); These factors make *M. morganii* an opportunistic pathogen that primarily causes urinary and wound infections [10], Diabetic mellitus causes a sever deregulation of immune response in a healthy human body [11]. The suppressed production of immune peptides and altered immune, susceptibility to infections are much higher in immunosuppressed patients with diabetes mellitus. The human host and microorganisms normally exist in a balanced relationship [12].

As diabetes is multifactorial, including genetic and environmental, and type 1 diabetes is an autoimmune disease, the current study focused on the role of bacteria in causing the

disease, and it may be the spark in the disease. This is because of the molecular mimicry between molecules present on the surface of bacteria and molecules present on the surface of the cells of the body, and that the antibodies in the body can attack the cells of the body and cause autoimmunity to type 1 diabetes instead of attacking the bacteria themselves.

2. MATERIAL AND METHODS

2.1 Study group

The specimens were collected from patients at Al-Kindi Educational Hospital in Baghdad, Iraq, which included complete information about the patients' examinations.

Age ranging from fewer 1 to 16 years, a total of sixty patients (35 female, 25 male), Patients with diabetes diseases diagnosed by a physician and control collected from fifty healthy with no signs of diabetes diseases (28 female, 22 male). Sixty samples of blood and urine were collected from patients. Serum discrete and kept at -20℃ until use for serological test and agglutination. Serological test: The serum Interleukin-17 levels were specified by the industrialist's directive of mercantile (ELISA) kits (Cusabio biotech /China).

2.2 Bacterial isolation

M. morganii, was isolated from the patient's urine. Microbes were the beginning of aerobic growth at 37℃. Sequence of biochemical assay that can be used to determine the morphology of bacteria. Finally, the entire isolates were diagnosed by the VITEK-2 kit.

Preparation of the bacterial antigen (Killing a complete bacterial cell with heat).

The cells were prepared using a method [13] to perform the agglutination test.

Antibodies Production from patients with type 1 diabetes.

The blood was taken from patients with diabetes, the serum was obtained after clotted for at least 30 minutes, then the blood is centrifuged for 30 minutes at 1500 RPM [14]. Serum is kept freezing at (-20℃) until use.

2.3 Agglutination antibodies with antigens

1. Totally wells are Cover via fifty µl (1. 50 x 10.0^8 CFU/milliliter) of *M. morganii*, Ag.
2. Sequential dilutions of the serum of patient immunoglobulin (1: 2, 1: 4, 1: 8, 1: 16, 1: 32, 1: 64, 1: 128, 1: 256) is included in each well.
3. Characterization of microscopic agglutination scale and estimate of microscopic agglutination [14, 15].
4. Recognized the assessed microscopically agglutination all analyses were done in replica with 3 repeats.

2.4 Production of anti- *M. morganii*, rabbit serum

An anti- *M. morganii*, (no. 2) serum was created at four rabbits. By chief Formalin destroyed cells are mixed with Freund's whole assistant inoculated at several locations of rabbit shadowed by 3 consequent promoter injections at week after week interims [16]. After that, the rabbit serum was collected, heat-inactivated (30 min, 58℃). The serum was distributed in Eppendorf tubes (1.5 ml) and stored at -20℃. Until used in the slide agglutination tests.

2.5 Slide agglutination assay

Slide agglutination assay of living cells for nine *M. morganii*. Performed with antiserum, the anti-serum is thinned at ten - time and twenty -time by SDW (sterile D.W.). Put 1 drop 10 times and 20 times of the anti-serum diluted with sterilized distilled water (SDW) on glass slides and one drop of physiological saline (PS) separately. After that, one drop of heat-killed cells was added in every droplet in slide. Lastly, it is pushed backward and backward for (5) min. The agglutination was then watched optically [16].

2.6 Measurement of cytokinetic levels in patients' serum

Determination of cytokine levels in the patient's serum. The concentration level of five types of cytokines in the serum of those included in the study was estimated and compared with healthy subjects (control group), IL-17A using enzyme-linked immunosorbent absorption method ELISA, and followed the method of work based on the principle of color discrimination resulting from the binding of specific antibodies to the antigen and the standard titration prepared by (British Pep Rotech Company). Kinetic concentrations were calculated by measuring the optical density of the studied kinetic properties in the serum of samples of patients with diabetes and the standard sample (healthy) using an ELISA device and the results of the studied samples were recorded by projection. The readings are on the standard curve for the purpose of extracting the included kinetic concentrations.

2.7 General ELISA test steps

1- Prepare a surface to which a known quantity of capture antibody is bound.
2- Block any nonspecific binding sites on the surface.
3- Add an antigen-containing sample to the plate.
4- Wash the plate, so that unbound antigen is removed.
5- A specific antibody is added, and binds to antigen (hence the 'sandwich, the Ag is stuck between two antibodies).
6- Add enzyme-linked secondary antibodies as detection antibodies that also bind specifically to the antibody's Fc region (non-specific).
7- Wash the plate, so that the unbound antibody-enzyme conjugates are removed.
8- Add a substrate that is converted by the enzyme into a color or fluorescent or electrochemical signal.
9- Measure the absorbance or fluorescence or electrochemical signal (e.g., current) of the plate wells to determine the presence and quantity of antigen.

3. RESULTS AND DISCUSSION

3.1 Study population

The total number of diabetic patients type -1 in this study was 60 composed of 25 males and 35 females. In addition, 50 apparently healthy controls from Baghdad area composed of 22 males and 28 females.

Table 1 shows an increase in diabetic patients with aging and as indicated by the age cluster it is seen that diabetic patients type-1 were prevail between people at age between 1-16 yr. (76.6%) in diabetic. The perceptions were companionable by those [17]. Expansion level of diabetic

patients among people higher than 10 yr. is because of hormonal variation on account of females which influence the immune [18]. Whereas the majority of men complain of hormonal variation when 13 years that increase glucose in blood [19], Furthermore, the phagocytic activities and the natural killer cells (NK) remarkably.

Table 1. Demographic data of diabetic patients type-1 and controls according to age

Types	Gender No. (%)		Age No. (%)			
	Males	Females	1-5	6 - 10	11-16	Total
Patients	25(41.6)	35(58.4)	9(15)	46(76.6)	5(8.4)	60
Controls	22(44)	28(56)	7(14)	41(82)	2(4)	50

Whose common patients are females because of the starring action of hormones expanding the opportunity for autoimmune disease presence because of the activation. Likewise, these outcomes are in concurrence with [20] who announced that the level of this infection in Tunisian was higher in females (8.6%) then point that of male (7.1%).

3.2 Bacterial isolation

Totally spaceman of urine is examined by (G.U.E) and the presence of bacteria was investigated by culture urine. The biochemical tests were performed to diagnose bacteria. This study showed that Coagulase negative, β Hemolysis, Urease positive and Novobiocin resistance positive. *M. morganii*, was isolated from urine of diabetes patients (n=9) 18%, which are shown in Table 2.

Table 2. Biochemical tests and isolation frequency for *M. morganii*, from urine samples of diabetic patients type-1

Sample		*Morganella morganii*
Biochemical tests	Pigment produce	Yellow
	Catalase	+
	Coagulase	-
	Oxidase	-
	Hemolysis	β
	Capsule Formation	+
	Lipase	-
	Urease	+
	Novobiocin resistance	+
Isolation frequency (urine)	No.	50
	Positive	9
	%	18

Table 3. The ability of *Morganella morganii* to ferment sugars isolated from different infections in diabetic patients

Lactose	-
Sucrose	-
Mannitol	-
Sorbitol	-
Ribose	+
Raffinose	-
Xylose	-
Mannose	D

Positive: +, negative: -, D: Weak

The immune pathogenesis of the inflammatory cascades of the disease was related with *M. morganii* [21]. However, diabetic is characterized via irregulation of the immune system and promotion of auto antibodies as well as, cellular infiltration of langerhans cells.

Morganella morganii was diagnosed by examining its ability to ferment sugars such as Sucrose, Lactose, Mannitol, Sorbitol, Ribose, Raffinose, Xylose, and Mannose as shown in Table 3.

3.3 Titration of antigen - antibodies

In Table 4 the results displayed serum with patients reaction with *M. morganii*, Ags (all cells) as 3 bacteria antigens agglutinated in caliber 1:64 and three in caliber 1:128 of patients serum (antibodies) whereas 1 and fife of *M. morganii*, antigens agglutinated in the patients serum in caliber 1:256 and 1:16 Consecutively.

Agglutination is based on the being of antibodies in the serum of patient, which has the ability to interact with specific antigens [22]. An Abs answer to an assumed Ag is symbolic of its term in vivo it can be utilized in subunit immunization or by way of a goal in inactive immune therapy or prevention.

The good old method to diagnose an infection is reflected in the positive interaction between antibodies and surface antigens about bacteria, the role of bacterial surface proteins is very important in bacterial interactions with the environment, cell-cell interactions, transport, cell signaling, and in antibiotic resistance; and in infection of host cells, especially to defend against host responses. Because of their direct interaction with the host immune system, some bacterial surface proteins may be used for vaccine development [23].

Table 4. Agglutination of antigens (whole cells of *M. morganii* against antibodies in sera of patients)

Concentration of cells of *M. morganii* antigens	No. of bacteria	Titer of antibodies *M. morganii*	Control (serum)
1.5×10^{8} (CFU/mL)	1	256	0
	2	128	
	3	64	
	4	128	
	5	16	
	6	64	
	7	64	
	8	128	

Table 5. Slide agglutination of 9 isolates of *M. morganii* with the anti- *M. morganii* rabbit serum

No. of isolates	Type of isolates	Agglutination Distribution of antiserum	
		10-fold	20-fold
6	M.1, M.2, M3, M4, M5, M.6	+	+
2	M.8, M.9	+	-
1	M.7	-	-

Usually *M. morganii*, have an informed ability to bond non-specially to simple polymer surface, this mixture could stop via shield the inner by changed proteins, vaccine otherwise like target in inactive immune therapy or preventive [24]. Thus, antigenic bacterial proteins certain are approaching goals of immunotherapy, that achieve obtainable an original stratagem aimed at regulator of bacterial infection and can perhaps decrease infection and require a significant outcome on people fitness. In this study is to find immunological indicators associated with the disease. The presence of anti-bacterial antibodies was confirmed in patients with diabetes mellitus.

3.4 Visibly agglutination (macroscopically) test

To identify the agglutination capacity slide agglutination exam (anti *M. morganii*, rabbit serum) was done (Table 5). Among 9 isolates, 6 isolates (M. 1, M. 2, M. 3, M. 4, M. 5, M .6) positive responded on the slide agglutination assay in 10- and 20-time dilutions of anti-serum (anti -bacteria rabbit serum). Two isolates (M.8 and M.9). Positive response in slide agglutination with lone 10 times weakening of serum, while there is no positive reaction with 20 times dilution of antiserum. Only one isolation (M.7) did not show a positive reaction in fold dilution of the antiserum 10 and 20 when testing the slide agglutination.

There are some isolates that gave a positive result of agglutination for both fold dilutions 10 and 20, and some of them gave a positive result only with fold dilution 10 and one isolation was a negative result in 10-20 Crease dilution serum in slide agglutination assay. Because of the varying environmental conditions and the contrast of the immune system.

3.5 Cytokinetic levels in patients' serum

Results the immune side the concentration levels of some cellular kinetics of the pro-inflammatory and anti-inflammatory precursors were studied in the serum of the studied samples using the enzyme-linked immunosorbent technology, ELISA Interleukin-17A (IL-17A) Concentration Level. The results showed a decrease in the concentration of IL-17A in the serum of infected patients compared to the control. The concentration in the serum of patients was 0.011 ± 0.019 (pg/mm), while its concentration in the control (healthy) was 0.007 ± 0.033 (pg/mm) (Figure 1). Stats results by the T-test experienced a significant variation in the concentration of IL-17A between patints with diabetes and the control sample and under the probability level $P<0.05$.

Several chronic inflammatory diseases are associated with the secretion of IL-17 by activated immune cells. The less inflammation in the body, the lower the production of interleukin-17, such as arthritis, psoriasis and dermatitis. It is lowered in people with diabetes when inflammation is reduced, and IL-17 receptors provide a signaling direction from the immune system to the tissues. IL-17A induces a sustained immune response in moderate to severe type 1 diabetes [8].

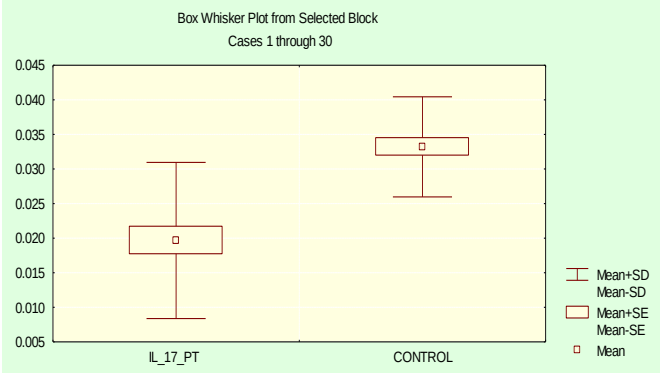

Figure 1. IL-17a concentration rate in the serum of the studied samples

Results in agreement with results of the study performed by [25], for obtaining significant differences in the level of Interleukin -17 in diabetes patients, while results it does not agree with the results of [26] because its results were without statistically significant differences in the level of interleukin-17 with diabetic patients [27] and it was clear that the level of interleukin-17 with diabetic - type 1 does not appear It is increased in patients, but most studies support the significant role that interleukin-17 plays in destruction of in beta cells trendy the pancreas of people with type 1 diabetes, in patients with type 1 diabetes, CD4 + T cell lymphocytes differentiate into Th17 tissue The pancreas contains k β-cells that destroy beta-cells by secreting IL-17, as well as CD4+ T-cells that can also differentiate into Th1 and Th2.

4. CONCLUSIONS

The *Morganella morganii* isolated from the urine of patients. With *M. morganii* (whole cell) antigens as three agglutinated bacterial antigens in different titers of patients' serum (antibodies) of *M. morganii* antigens accumulated in patients' serum. There are statistically significant differences between this interleukin-17 between patients and the control sample in the serum of patients compared to the control sample. A decrease in the cytokinetic concentration, compared to the control sample in the affected blood serum. Identification of the agglutination capacity of a slide agglutination test (Anti-*Morganella morganii* rabbit serum). Observation of the agglutinating capacity between bacteria as antigen, diabetic serum and bacteria-injected rabbit serum, the results showed the ability of the killed antigen bacteria isolated from diabetic patients to agglutinate with their serum, and its ability to agglutinate with the serum of rabbits injected with these bacteria.

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