The association between gastric bacterial infection and low level of vitamin D among patients with type 2 diabetes mellitus

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ABSTRACT

Objectives: The present research aimed to find an association between infection by Helicobacter pylori and vitamin D deficiency in type 2 diabetic Iraqis attending Al-Yarmouk Teaching Hospital.

Methods: According to fasting blood glucose, the samples were divided into a non-diabetic group with ten diabetic individuals and a diabetic group with thirty individuals.

Results: The anti- H. pylori (IgG) levels were 86.77±58.62 NTU/μL in diabetic patients compared with 10.12±7.40 NTU/μL in non-diabetic group. Vitamin D levels were decreased significantly in infected patients compared to non-infected subjects.

Conclusion: The H. pylori-infected patients have recorded the lowest level of vitamin D than non-infected individuals.

Keywords bacterial infection, diabetes mellitus, H. pylori, vitamin D deficiency

INTRODUCTION

Diabetes is a metabolic disorder distinguished by hyperglycemia, resulting from weaknesses in secreting insulin, insulin functions, or both. Long-lasting hyperglycemia is fully linked with long-term damage and dysfunction of various organs, particularly blood vessels, kidneys, eyes, nerves and heart. Many pathogenic processes play a major role in developing diabetes, ranging from pancreatic beta-cell autoimmune dysfunctions to a deficiency in producing insulin that may lead to insulin resistance. The main malfunction in diabetes is insulin not absorbed by the target tissue for carbohydrate, fat, and protein break down. This may also happen as a result of inadequate insulin secretion. The patients with diabetes fall into two types: type I and type II. In type I, patients are at risk of developing an autoimmune pathologic process, which occurs in Langerhans’ islets and genetic markers. In type
II, diabetes can create in resistance to insulin action.\textsuperscript{1–3} \textit{H. pylori} about 2.5-3 \textmu m helical gram-negative bacteria.

Moreover, that type of bacteria found in 80% to 90% of gastritis patients and thought to be the main factor for developing gastric ulcers. Furthermore, \textit{H. pylori} and the diabetic link is inconsistently reported.\textsuperscript{4–6} A low level of vitamin D is predominant in older individuals due to short-time exposure to sunlight; it may lead to a lack of ability to do routine homework, weight gain, dark skin colour and defect in metabolism activity.\textsuperscript{7,8} Vitamin D related to many genes directly or indirectly, cell proliferation, differentiation, apoptosis, and angiogenesis.\textsuperscript{9,10} Muscle weakness, vitamin D deficiency is also associated with increasing the probability of different infectious and autoimmunity and malignancy.\textsuperscript{11} In addition to that, vitamin D possesses an anti-inflammatory property; thus, it controls cell proliferation and differentiation.\textsuperscript{12} Newly research suggested regulating the expression of specific endogenous antimicrobial peptides in immune cells control by vitamin D, which explain a vital part of vitamin D in modulating the immune response to various infectious diseases. Vitamin D may prevent infection risk by many mechanisms; vitamin D boosts innate immunity by modulating cytokine response.\textsuperscript{13} Vitamin D helps monocytes and macrophages activities by contributing to a potent systemic antimicrobial effect.\textsuperscript{14}

\textbf{MATERIALS AND METHODS}

\textbf{Subjects and parameters}

Forty subjects have participated in this study who attend Al-Yarmouk Teaching Hospital in Iraq, Baghdad, from April 2017 to July 2017. Thirty patients (twenty-three females and seven males) and ten healthy individuals (six females and four males) as a control group. They were all subjected to a personal interview to fill a specialized questionnaire form. Estimating blood glucose was done using a glucose oxidase with an alternative oxygen acceptor method.\textsuperscript{15} Serum 25-OH D vitamin levels were measured via the enzyme-linked immunosorbent assay (ELISA) where the detection of anti–\textit{H. pylori} IgG Antibody by ELISA method using NovaTec kit (Germany)—using enzyme-linked immunosorbent assay (ELISA) and detecting Immunoglobulin A (IgA) and Immunoglobulin G antibodies which developed against particular virulence proteins of \textit{H. pylori} by using western Blotting technique. After contacting with \textit{H. pylori}, patients might display antibodies from Immunoglobulin A, Immunoglobulin G and Immunoglobulin M classes against \textit{H. pylori} in the serum.

Moreover, after a few weeks, Immunoglobulin A antibodies typically form and remain detectable for a period that can be for a long time. Positive Immunoglobulin A results correlate well with the activity of gastritis. Nevertheless, those antibodies are locally formed and cannot always be detected in the serum. Immunoglobulin G antibodies are often first detected after IgM titer has decreased and can continue for many years. The rise in Immunoglobulin G titers refers to a \textit{H. pylori} infection has reached phase. High Immunoglobulin A antibody titers is a sign of chronic infection.
Moreover, Immunoglobulin M (IgM) antibodies form a few days after coming into contact with *H. pylori*. After a few weeks, the specific Immunoglobulin M could no longer be detected. In treatment monitoring, identifying specific Immunoglobulin M (IgG) antibodies against *H. pylori* is appropriate for confirming that the pathogen is eradicated. A significant decrease in the Immunoglobulin G (IgG) antibody titer approximately six months after treatment is seen as a success sign.

**Statistical analysis**

Results were analyzed using the SPSS and chi-squared test, and Fisher's exact test was necessary. Calculating the odds ratio and 95% confidence interval are conducted as well. The differences are significantly considered a 5% probability level.

**RESULTS**

According to the measurement of blood glucose can, we divide the study individuals into two main groups: healthy group 10 individuals (six females and four males) were subjected to anti-*H. pylori* antibodies detection, and they recorded four positive results (three females and one male) also the level of vitamin D were measured and recorded lowest level than non infected with *H. pylori*. While the second group is patients group 30 individuals (twenty-three female and seven males ) subjected to antibody detection of *H. pylori*, twenty-four individuals were positive results (nineteen females and five males ), and the infected individuals have recorded the lowest level of vitamin D than non-infected individuals.

| Table 1 Fasting blood glucose concentration (mg/dL) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Female          | Male            | Sig.  | P-value | CI 95%          |
| Control        | 89.66±11.94     | 92.50±20.20     | NS    | 0.99    | -102.8 to 108.4 |
| Diabetic Patients | 304.54±81.45   | 302.85±71.11    | **   | 0.99    | -72.69 to 69.31 |

*p*-value ≤0.01; NS: Non-significant

**DISCUSSION**
The results showed that the infection with *H. pylori* is more prevalent in diabetic patients are in agreement with previous findings. There are many lines of evidence to the high susceptibility of diabetics patient for infection, which can be listed as follows:

Diabetes induces deficiency in cellular and humoral immunity may increase the risk of *H. pylori* infection.

Diabetes may cause a decrease in acid secretion and gastrointestinal motility that stimulate colonization of pathogenic bacteria and increase the gut’s infection rate.

Alteration glucose metabolism can cause a chemical change in gastric mucosa, which helps establish *H. pylori* infection. Diabetes patients are sensitive to exposure to pathogenic microorganism than healthy individual.

Diabetic patients are more sensitive to exposure to pathogenic microorganism than their healthy individuals.

Several further factors likely play a significant role in the correlation between *H. pylori* infection with diabetes. Just like lifestyle is a more important cause of chronic infection with *H. pylori* and type II diabetes mellitus. It is shown that aged people with a good lifestyle have no risk to developed diabetes. Due to *H. pylori* infection, the stomach and duodenum diseases can hold back gastric emptying, hypothesized to cause a disparity between insulin initiation and carbohydrate absorption in diabetes children who have insulin-dependent.

Though, that delayed gastric emptying is a potential benefit, rather than a defect, concerning glycemic control in type 2 diabetes mellitus patients who were not given insulin as a therapy, and others assert that infection with *H. pylori* does not affect the emptying rate of the gastric regarding people with diabetes.

Infection with *H. pylori* may relate to the activating of platelet and its aggregation, increased lipid peroxides, producing reactive oxygen species production and homocysteine.

**Table 2** Anti *H. pylori* (IgG) concentration (NTU/μL)

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>Sig.</th>
<th>P-value</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>15.92±5.92</td>
<td>10.12±7.40</td>
<td>NS</td>
<td>0.9782</td>
<td>-78.04 to 66.43</td>
</tr>
<tr>
<td><strong>Diabetic patients</strong></td>
<td>86.77±58.62</td>
<td>106.00±33.75</td>
<td>NS</td>
<td>0.5893</td>
<td>-29.08 to 67.54</td>
</tr>
<tr>
<td>Sig **</td>
<td>**</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value **</td>
<td>0.0054</td>
<td>0.0059</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CI 95%</td>
<td>-122.1 to -19.55</td>
<td>-166.0 to -25.74</td>
<td></td>
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</table>

**p-value ≤0.01; NS: Non-significant**

**Table 3** Vitamin D levels (ng/mL)

<table>
<thead>
<tr>
<th></th>
<th>Mean ±SD</th>
<th>Significance</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>14.7±3.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Positive infected patients</strong></td>
<td>9.5±2.5</td>
<td>S</td>
<td>0.045</td>
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</table>
When insulin secreted in low concentration, it is considered one of the main pathophysiology-related defects in type II diabetes mellitus. Progress from regular glucose tolerance to prediabetes and type II diabetes mellitus distinguished by continuous defects in the \( \beta \) cell function.\(^{26}\) In addition to that, Rahman et al.\(^ {27} \) also described a positive link between the infection of \( H. \) pylori and poor secretion of insulin. Pancreatic \( \beta \)-cells, which release insulin, are particularly vulnerable to damage due to inflammation and oxidation,\(^ {28}\) so it is reasonable that inflammation due to the infection occurring in \( H. \) pylori leads to insulin secretion deficiency. When insulin secreted in low concentration, it is considered one of the main pathophysiology-related defects in type II diabetes mellitus. Progress from regular glucose tolerance to prediabetes and type II diabetes mellitus distinguished by continuous defects in the \( \beta \) cell function. In addition to that, Rahman, et al. also describes a positive link between the infection of \( H. \) pylori and poor secretion of insulin. Pancreatic \( \beta \)-cells, which release insulin, are particularly vulnerable to damage due to inflammation and oxidation, so it is reasonable that inflammation due to the infection occurring in \( H. \) pylori leads to insulin secretion deficiency.

Furthermore, Hsieh et al.\(^ {29} \) found that patients suffering from \( H. \) pylori infection are increasingly likely to have poor insulin secretion at an early age, increasing the probability of developing type 2 DM. A great deal of scientific evidence indicates that cytokines contribute to \( \beta \)-cell activity loss. Long-lasting exposure to Interleukin 1 beta, TNF-\( \alpha \), and IFN-\( \gamma \) participates extensively in inhibiting insulin secretion and stimulates \( \beta \) cells' apoptosis.\(^ {30,31} \) \( H. \) pylori infection induce mitochondrial-dependent apoptosis by the action of vacuolating cytotoxin in individuals who are contract diabetes by down-regulating anti-apoptotic Bcl-2, and upregulating pro-apoptotic Bax, increasing the activation of caspase-9 and -3.\(^ {32}\) Regardless of this research, many future studies are required to clarify the infection with \( H. \) pylori in insulin secretion and the incidence of type 2 diabetes mellitus.

As a result, it shows female more vulnerable to be infected with \( H. \) pylori and more sensitive diabetes depend on hormone response and many factors that make the female more infected than the male. In contrast, many studies did not report this association, the same as in.\(^ {33,34} \) On the other hand, the hypothesis of \( H. \) pylori infection can lead to a rising risk of development of diabetes in an infected individual. In some studies, diabetic patients are more likely to be infected with \( H. \) pylori, which can have an essential role in this area; some research suggests that \( H. \) pylori infection is more suitable for developing diabetes.\(^ {35}\) On the other hand, individuals infected with \( H. \) pylori have been recorded a low level of vitamin D compared with non-infected individuals; the explanation of this is that \( H. \) pylori effect on D vitamin receptor both at the tissue and the cell levels.\(^ {36}\) Surmeli et al.\(^ {37} \) proposed the incorporation of D vitamin to the treatment protocol of some infectious diseases lead to improve the treatment course.

Some researchers consider a low level of vitamin D to become a risk factor for infection with \( H. \) pylori and cause the failure of its treatment and suggested that to add vitamin D as a therapy to help in the eradication of infection because of antimicrobial effect and played a vital role in gastric mucosa homeostasis and host protection against infection with \( H. \) pylori.\(^ {38,39}\)
In conclusion, there is an association between *H. pylori* infection and low vitamin D level and diabetes mellitus type II development. Individuals with diabetes mellitus are more likely to be infected with *Helicobacter*; this means it is more susceptible to being infected. It is required for many studies to improve that relationship and also needed to use a high number of patients and different ages.

**ACKNOWLEDGMENTS**

None.

**DECLARATIONS**

**Authors’ contributions**

All authors have equally contributed to this work.

**Conflict of interest**

None.

**Ethical approvals**

Al-Nahrain University, College of Medicine and its Institutional Review Board approved the current study.

**Data availability**

Data can be requested from the corresponding author on reasonable request.

**Funding resources**

Nil.

**REFERENCES**


