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ORIGINAL RESEARCH ARTICLE

The Effect of Body Mass Index on the KYN/TRP Pathway in the Pathogenesis of Periodontitis

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Abstract

Purpose: The tryptophan–kynurenine (TRP-KYN) pathway is associated with inflammation, and kynurenine pathway (KP) dysregulation is present in overweight and obesity. Meanwhile, obesity and periodontitis are two of the most frequent noncommunicable illnesses, and epidemiological studies show that obesity has a role in the initiation and progression of periodontitis. However, the association between elevated body mass index and KP on periodontal disease etiology is unknown. As a result, our study aims to investigate the possible relationship between TRP/KYN ratio and body mass index (BMI) relationship in periodontitis.
Materials and Methods: The study comprised 20 periodontitis patients (P, Generalized Stage III Grade B, n=20) and 20 healthy persons (C, n=20). Clinical parameters (Bleeding index on probing (BOP), clinical attachment loss (CAL) and pocket depth (PD)), and BMI were recorded at the beginning of the study. Salivary and serum KYN/TRP ratios were analyzed using mass spectrometry–liquid chromatography (LC-MS/MS).
Results: Clinical periodontal parameters were statistically significantly higher in P group than in C group ($p<0.05$). While there was no change in serum KYN/TRP ratio across groups, salivary KYN/TRP ratio decreased in Group P compared with Group C ($p<0.05$). The salivary KYN/TRP ratio was positively correlated with the serum KYN/TRP ratio. At the same time, it showed a strong negative correlation with BOP, a moderate correlation with PD and CAL, and lower negative correlation with BMI.
Conclusions: KP dysregulation due to obesity may increase the risk of developing periodontal disease.

Key words: Periodontitis; Obesity; BMI; KYN/TRP; Tryptophan; Kynurenine

Introduction

Tryptophan, an essential amino acid for human metabolism, is involved in the biosynthesis of significant substances such as neurotransmitters, neurohormones, and niacin.[1,2] 90% of the metabolism of tryptophan is carried out via the oxidation process, commonly known as the kynurenine pathway (KP) (Figure 1).[3] Tryptophan, which differs in tissue and cell localization and substrate specificities, is converted to N-formyl kynurenine by enzymes called tryptophan 2,3-dioxygenase (TDO) and indolamine 2,3-dioxygenase (IDO).[4] While IDO acts locally and modulates tryptophan levels in response to inflammation, TDO acts systemically by regulating blood tryptophan levels.[5] Other catabolic pathway enzymes contribute to generate the metabolites of this pathway, which are biologically active and affect cellular activities in physiological and pathological ways.[4] Under physiological conditions, KP is tightly regulated but changes when the immune system is active. KP dysregulation has been associated with several diseases, including cardiovascular diseases,[6–8] depression,[9,10] inflammatory bowel disease,[11] diabetes,[12] schizophrenia,[13] neurodegenerative disorders,[14] cancer[15,16] and multiple sclerosis.[6]

Obesity and periodontitis are two of the most prevalent noncommunicable illnesses, and epidemiological studies show that obesity has a role in periodontitis initiation and progression.[17] Obesity is recognized to have a chronic low-grade inflammatory state, which is also a prevalent factor in obesity-related diseases.[18–21] Furthermore, metabolites such as amino acids are variables that interact with processes involved in metabolic balance.[19,21,22] The catabolic pathways of tryptophan appear to be particularly important since they are controlled by dietary and inflammatory signals and are connected to metabolic control and management of calorie intake.[23–25] Under normal physiological conditions, TDO performs over 90% of tryptophan metabolism in the liver, but KP may also be activated extrahepatically by IDO driven by inflammatory signals associated with obesity.[23,26–31] The extrahepatic IDO activity is commonly expressed or reflected by the KYN/TRP ratio.[26]

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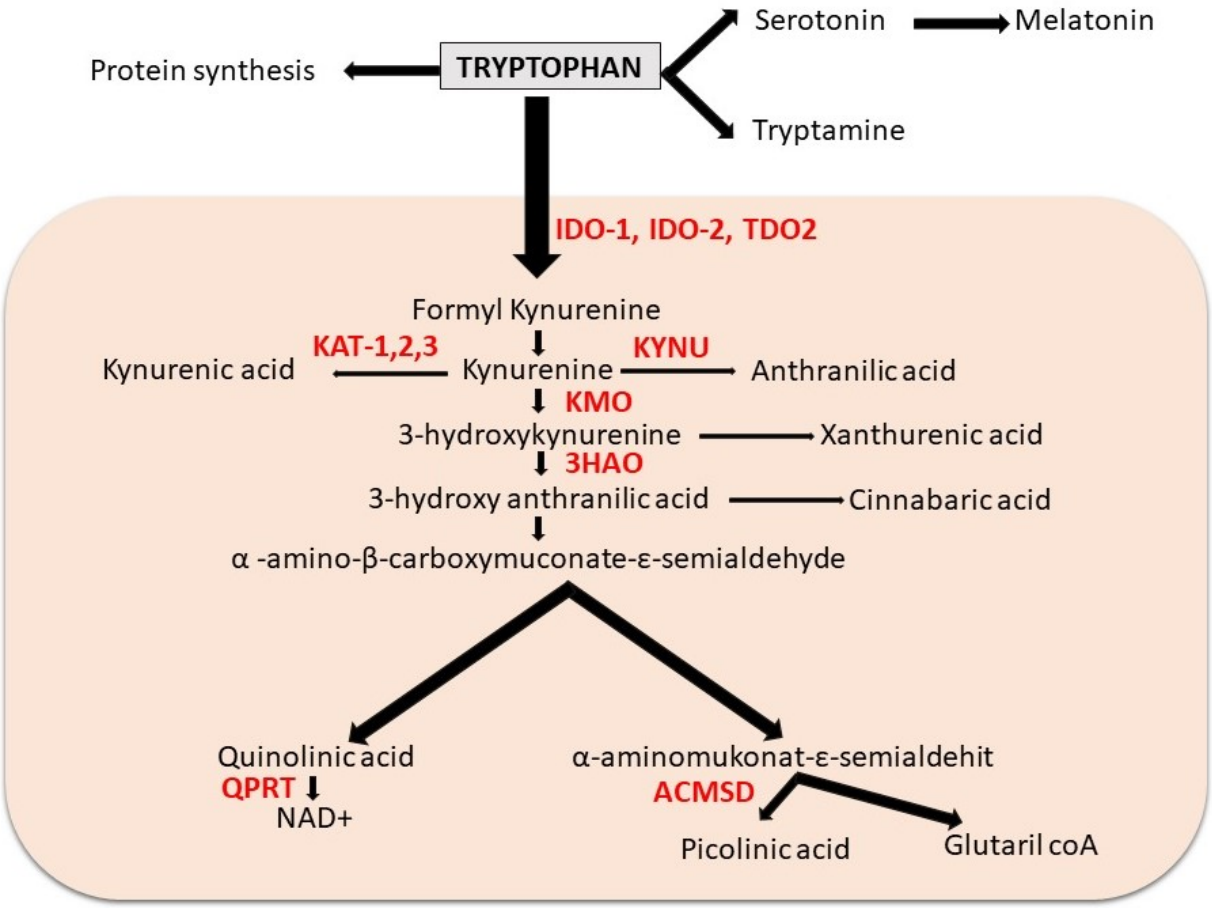

Figure 1. Tryptophan pathway. IDO: indolamine 2,3-dioxygenase; KAT: kynurenine aminotransferase; KYNU: kynureninase; 3-HAO: 3-hydroxy anthranilate 3,4-dioxygenase; QPRT: quinolinic-acid phosphoribosyl transferase; ACMSD: 2-amino-3-carboxymuconate semialdehyde carboxylase.

According to a few studies, KP is additionally related to periodontitis. [9,10,32] However, there is no study in the literature investigating the effect of increased KP activation associated with BMI and the impact of this interaction on the risk of periodontitis development. In the light of all these literature findings, our study hypothesizes that as the BMI increases, KP activation will increase, increasing the risk of periodontal disease development. Our study aims to evaluate the salivary and serum kynurenine/tryptophan (KYN/TRP) ratio change between periodontal inflammation.

Material and Methods

Study Design

The study included twenty periodontitis patients (Group P, Stage III, Grade B, n=20; 11 females, 9 males; mean age: 41.56 ±10.56 years) and twenty periodontally healthy individuals (Group C, n=20; 8 females, 12 males; mean age: 39.56±6.51 years) who applied to Ankara University Faculty of Dentistry, Department of Periodontology. The Helsinki Declaration conducted the study, which was approved by the Ankara University Faculty of Dentistry Human Research Ethics Committee (No: 9/1, on 08.01.2011). All individuals who agreed to participate in the study signed a valid informed consent form. The periodontal diagnosis was based on the World Workshop on Periodontal and Peri-Implant Diseases and Conditions (2017). [33] At stage III, periodontitis has significantly damaged the attachment apparatus, and tooth loss may occur without advanced treatment. The stage is characterized by deep periodontal lesions extending to the middle portion of the root and whose management is complicated by the presence of deep intrabony defects, furcation involvement, and history of periodontal tooth loss/exfoliation. Periodontitis may progress with different rates in individuals, respond less predictably to treatment in some patients, and may or may not influence general health or systemic disease. Grade B shows a moderate rate of progression, and destruction is commensurate with biofilm deposits. [33] Periodontitis was diagnosed in patients with at least 16 natural teeth (excluding third molars) who exhibited interdental radiographic bone loss $\geq$2 in non-adjacent teeth and probing depth (PD)>3 mm in at least two teeth.

Periodontitis Stage III, Grade B was diagnosed using the following conditions:

- Radiographic evidence of alveolar bone loss extending to middle third of the root and beyond.
- Number of tooth loss due to periodontitis $\leq$4
- Teeth involved$\geq$%30
- $\geq$5 mm interdental clinical attachment loss (CAL)
- 0.25<% bone loss/age <1.

Individuals without a symptom or no history of periodontal disease, clinically periodontal health (bleeding on probing (BOP) <10%, PD <3 mm), and well-maintained dental hygiene were designated as controls. An expert periodontist (SMA) performed all measurements from six sides of each tooth. Pregnant and lactating mothers, obese individuals, smokers, patients with systemic disorders including diabetes, cardiovascular disease, and cancer, antibiotics or anti-inflammatory drug usage, or medication with calcium channel blockers, phenytoin, or cyclosporine, or patients who had received periodontal therapy during the previous three months were all excluded.

Table 1. Comparison of Demographic and Clinical Periodontal Parameters Between the Groups

Clinical Parameters	Control (C; n=20)	Periodontitis (P; n=20)
Age (year)	38.00 (35.75-40.5)	40.50 (34.75-48.50)
Gender (n, f/m)	12/8	9/11
PD (mm)	1.59 (1.44-1.64)	2.83 (2.42-2.96)*
BOP (%)	5.30 (3.70-1.50)	42.00 (31.38-60.45)*
CAL (mm)	0.00 (0.00-0.00)	3.02 (2.83-3.37)*
BMI	21.20 (20.63-23.30)	26.10 (21.78-28.46)*

PD: probing depth; BOP: bleeding on probing; CAL: Clinical attachment lost; BMI: body mass index Data as median-interquartile range. Mann-Whitney U test was used. * Statistically significant difference (p<0.05)

Saliva and Serum Samples

Unstimulated saliva was obtained after a 12-hour fasting period in the early hours (9:00 am to 11:00 am). Whole saliva (approximately 2 ml) was collected using sterile polypropylene tubes. The samples were centrifuged at 2800 ×g for 10 minutes. [34]

Venous blood samples were collected from antecubital vein by venipuncture. The samples were centrifuged at 4000 ×g for 10 minutes. The saliva and blood samples were kept at -80°C until analysis. [34]

Analysis of KYN/TRP

The salivary and serum KYN and TRP levels were determined using mass spectrometry–liquid chromatography (LC-MS/MS, ESI Source, Thermo Scientific Accessmax), a method modified from Di Gangi et al. [35]

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 (SPSS v.22, IBM SPSS Inc., Chicago, IL, USA) program. Shapiro Wilk test was used to evaluate the normal distribution. Mann-Whitney-U test was used for intergroup comparisons of independent variables, whereas Student-t test was used for dependent variables. Spearman correlation was performed to test the relationship between groups. All tests have been conducted with a significance level of α=0.05.

Results

Clinical Parameters

Table 1 shows demographic and clinical periodontal characteristics. The clinical periodontal parameters in P group were considerably higher than C group (p 0.05). Regarding BMI, age, and gender, there was no significant difference between groups (p=0.997, p=0.706, and p=0.100, respectively).

Biochemical Parameters

Table 2 presents the serum and salivary KYN/TRP ratio. When the KYN/TRP ratios between the two groups were compared, only the salivary levels were different, and the C group was statistically significantly higher than the P group (p<0.001).

Table 2. Saliva and serum KYN/TRP ratio in periodontitis and control groups

Biochemical parameters	Control (C; n=20)	Periodontitis (P; n=20)
KYN/TRP ratio (saliva)	0.05 (0.03-0.14)*	0.02 (0.02-0.03)
KYN/TRP ratio (serum)	0.04 (0.03-0.04)	0.04 (0.04-0.05)

Data are expressed as median-interquartile range. Mann Whitney U Test. * Statistically significant difference (p<0.05)

Correlation of Periodontal and Biochemical Parameters

The association coefficients between periodontal clinical markers and salivary and serum KYN/TRP ratios are shown in Table 3. Serum KYN/TRP ratio positively correlated with BOP and BMI (p<0.05). Salivary KYN/TRP ratio was negatively correlated with BMI and clinical periodontal parameters (p<0.05). Serum and salivary KYN/TRP ratios had a significantly negative correlation (p<0.05).

Discussion

Our study aimed to evaluate the change in BMI and KP activity in periodontitis. The salivary KYN/TRP ratio was statistically significantly higher in C group compared to P group, consistent with our hypothesis, and KP activity decreased as the BMI index increased.

The KP pathway is the primary TRP metabolism pathway. Inflammation or immunological activation of the IDO enzyme causes the extrahepatic KP to activate, which causes the accumulation of TRP metabolic end products. [36,1,37] As far as we know, no published research has investigated the connection among BMI and KP in periodontal inflammation. We compared the salivary and serum KYN/TRP ratio, which indicates IDO activation, [26] between age, gender, and BMI-matched stage III periodontitis patients and periodontally healthy people based on this information.

The enzyme IDO regulates immunity and inflammation by degrading TRP into KYN and other metabolites (Figure 2). [38] A decrease in TRP via IDO-activated Tregs and suppressed Th17 cells has previously been demonstrated to reduce proinflammatory responses in various inflammatory disorders. [39,40] Several cell types have anti-inflammatory properties through inducing IDO expression. [41] As a result, IDO plays a vital role in controlling inflammation in specific contexts, either by preventing inflammation and maintaining the suppressive phenotype of Tregs when IDO is active or by permitting unregulated inflammation and Treg reprogramming when IDO is absent. As a result, our study reveals that the KYN/TRP ratio decreased with periodontal inflammation. This can be interpreted as a decrease in IDO activity and an increase in the expression of proinflammatory cytokines. Consistent with our results, Hao et al. also showed that P.gingivalis, which is a crucial periodontopathogen, reduces IDO expression in gingival samples. [42] Indeed, Palm et al. demonstrated that P. gingivalis and its gingipains inhibited IDO expression in human gingival fibroblasts, decreasing the host response and possibly further developing P. gingivalis pathogenicity against host immunity. [43] Considering the immune nature of periodontal disease, reduction of IDO expression and/or activity, an immunomodulatory mechanism, may serve host-induced periodontal tissue destruction.

The blood concentration of TRP declines in diseases like HIV infection, neurological disorders, and cancer whereas KYN and other TRP catabolites concentrations rise. [44,45] However, no change in serum KYN/TRP ratio was identified in our investigation. In contrast to our findings, Kurgan et al. [32] reported that the serum KYN/TRP ratio was higher in control group than in periodontitis group and no change in the salivary KYN/TRP ratio between groups. They stated that a large amount of TRP is released into the saliva

Table 3. Correlation of biomarkers between clinical periodontal parameters

Variables	Sex	BMI	PD	BOP	CAL	KYN/TRP ratio (serum)	KYN/TRP ratio (saliva)
KYN/TRP ratio (serum)							-0,364*
Age	0,333*	0,278	-0,019	0,114	0,142	0,257	-0,099
Sex		0,297	-0,028	0,154	-0,020	0,232	-0,262
BMI			0,170	0,247	0,133	0,418*	-0,399*
PD				0,858**	0,886**	0,297	-0,515*
BOP					0,783**	0,363*	-0,605**
CAL						0,299	-0,443*

BMI: Body mass index; PD: probing depth; BOP: bleeding on probing; CAL: Clinical attachment lost; KYN: Kynurenine; TRP: Tryptophan. Values in bold are different from 0 with a significance level alpha <0.05 (Spearmen correlation test *p<0.05; **p<0.001) r = 0.20–0.40 positive and low correlation. r = 0.40–0.60 positive and mild correlation. r = 0.60–0.80 positive and high correlation.

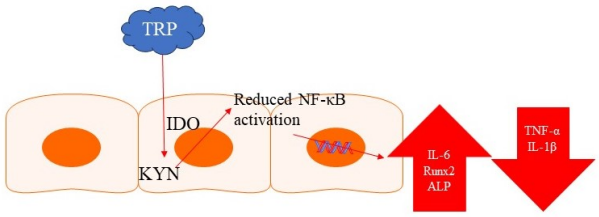

Figure 2. Anti-inflammatory effect of KYN/TRP pathway. TRP: tryptophan; KYN: kynurenine; IDO: indolamine 2,3-dioxygenase; NF-κB: nuclear factor kappa B; IL-6: interleukin 6, Runx2: Runt related factor 2; ALP: alkaline phosphatase; TNF-α: Tumor necrosis factor alpha; IL-1β: interleukin 1 beta.

due to enhanced vascularization and protein breakdown in periodontal inflammation. An increase in blood capillaries in gingival connective tissue produced by periodontal inflammation, as well as a rise in gingival crevicular fluid, might explain increased salivary TRP levels. In addition, the inflammation process damages the protein structures in the periodontium, which raises the number of amino acids in saliva. A similar circumstance existed in our study and may have contributed to the lower KYN/TRP ratio.

Obesity is a chronic condition that impairs both general and oral health.[46,47] The physiological and molecular processes that may explain the link between obesity and periodontitis are systemic inflammatory alterations in proinflammatory cytokines, hormones, and oxidative stress marker levels. These changes may increase susceptibility to infections and chronic inflammatory diseases.[48–50] Numerous epidemiological studies have demonstrated the connection between periodontal disease and obesity. Obese people had a higher odds-ratio for periodontitis than non-obese people, according to a cross-sectional analysis.[51,52] However, in our study, no statistically significant difference was found in BMI values across the groups; in the P group, BMI was higher than in the C group. Compared with the literature, the salivary KYN/TRP ratio is lower in the P group than in the C group. While the KYN/TRP ratio in the vascular circulation decreases due to low-grade systemic inflammation due to periodontitis, the increased BMI index, which also causes systemic inflammation, may cause an increase in the KYN/TRP ratio. Ultimately, the cumulative effect of these two diseases may have prevented a visible change in the KYN/TRP ratio. Because it is known that obesity increases the serum KYN/TRP ratio[53] and causes low-grade chronic inflammation.[20] Therefore, in periodontitis where the local inflammatory response is active, the ratio of KYN/TRP in saliva, which contains gingival crevicular fluid and serum, decreases in parallel with the inflammatory response. In addition, it can be interpreted as the increased dietary intake of TRP and the decrease in IDO activity due to increased BMI, resulting in no difference between the groups.

Our study is essential in showing the possible interaction between increased BMI and periodontitis and the effects of these diseases on systemic health. However, the main limitation of our study is that there was no difference between the groups in terms of BMI. Clinical prospective investigations need to be conducted in which groups with different BMI are created and obese individuals are included. Further studies will be precious in showing the effect of possible TRP intake on oral and systemic health, its effect on periodontal disease on systemic health, and the interaction between obesity and periodontitis.

Conclusion

As a result of our study, in which we aimed to evaluate the effects of periodontal inflammation and obesity on KP activity, it can be concluded that IDO activity decreased in the P group and is compatible with host-induced tissue destruction. Although the increase in BMI index reduces IDO activity, the increase in the amount of TRP taken with the diet will also increase the metabolism of this protein. In this context, although IDO activity, which acts locally, decreases with obesity, it can be thought that KP continues its pro-inflammatory activity through other possible metabolic pathways. However, further studies are needed to evaluate the intergroup variation in obese and non-obese P and C groups.

Author Contributions

All authors have made substantial contributions to conception and design of the study. ZG and SMA have been involved in data collection, data analysis and interpretation, drafting the manuscript and revising it critically and have given final approval of the version to be published.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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