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Duration of Type II DM, HbA1C Levels, TNF-α and IL-10 as Risk Factors for Level Charcot Joint Foot and Ankle in Type II DM Patients

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ABSTRACT

Introduction: Type II Diabetes Mellitus has complications including disorders of the musculoskeletal system or what is often called diabetic charcot joint or charcot neuroarthropathy. Various risk factors are thought to increase the incidence of Charcot joint foot and ankle. Various studies have been made to assess these risk factors with the aim of reducing the occurrence of these complications.
Material and Methods: The study used an analytical observational design with a case study and control approach to determine whether Type II DM II ≥ 10 years, HbA1c levels II ≥ 7%, TNF-α levels II ≥ 1.0 ng/L and IL-10 levels ≤ 255 pg/mL as factors. risk of Charcot joint foot and ankle in Type II DM patients. Where the sample involves 24 case groups and 24 control groups. Then a descriptive analysis was performed, bivariate inferential analysis using the chi-square test and an assessment of the risk factor odds ratio (OR). Then multivariate analysis was performed to assess the strength of the influence of risk factors using logistic regression test
Results: There is a significant difference between Type II DM II ≥ 10 years, HbA1c levels II ≥ 7%, TNF-α levels II ≥ 1.0 ng/L, and IL-10 levels ≤ 255 pg/mL which are risk factors for the occurrence of charcot joint foot and ankle in Type II DM patients. The duration of type II DM II ≥ 10 years had the strongest relationship while IL-10 ≤ 255 pg/mL had the weakest relationship for the occurrence of Charcot joint foot and ankle in Type II DM patients.
Conclusion: Increased duration of Type II DM, HbA1c level and TNF-α level above certain level and low IL-10 amount are risk factor for Charcot joint foot and ankle in Type II DM patients, with the duration of type II DM being the strongest risk factor.

Keywords: Diabetes mellitus type II, charcot joint foot and ankle, risk factors

INTRODUCTION

Diabetes mellitus (DM) is a major health problem, with the people living with it are increasing over time. Data from global studies show that the number of people with diabetes mellitus in 2011 has reached 366 million people, and it is expected to increase to 552 million by 2030.[1] If not properly treated, DM can cause various complications affecting numerous organs such as the heart, eyes, kidneys, blood vessels, nerves and even the musculoskeletal system. Charcot Neuroarthopathy (CNA) is a complication of diabetic neuropathy, which is characterized an inflammatory process that can lead to damages in the bones and joints, affecting the shape and function of the foot.[3]

There are several risk factors for developing CNA in patients with DM, such

as age, gender, duration of diabetes mellitus and levels of HbA1c. Several studies have shown that increased HbA1c levels play a significant role in peripheral neuropathy which is associated with occurrence of CNA. However, since CNA is a chronic inflammatory process, there are some factors contributing to it, such as pro inflammatory cytokines (IL-1). This inflammatory cascade has an effect in increasing bone resorption by elevating osteoclast activity which can lead to CNA in people with DM. Therefore, it is important to know the risk factors for the occurrence of CNA in diabetes mellitus patients so that prevention can be done earlier in order to reduce the incidence of CNA in patients with DM.[4,5]

This research aims to know the relationship between the incidence of Charcot Neuroarthropathy and the duration of Type II DM, HbA1c levels, TNF-α levels and IL-10 levels in Type II DM patients.

MATERIAL AND METHODS

This research is an analytic observational study with a case control study to analyze if Type II diabetes is ≥ 10 years, HbA1c levels ≥ 7%, TNF-α levels ≥ 1.0 ng / l and IL-10 levels ≤ 255 pg / ml as a risk factor for charcot joint foot and ankle in Type II DM patients. This research was conducted Sanglah General Hospital Denpasar, from February 2021 until August 2021. The research protocol for Ethical Clearance from the Research Ethics Commission at the Faculty of Medicine, UNUD / Sanglah Hospital Denpasar was submitted before the research was carried out. Subjects were given an explanation of the purpose of the study and were asked to fill out written informed consent

The incidence of foot and ankle charcot joints was done clinically and the investigations were assessed with plain radiographs. The case group is comprised of type II DM patients suffering from charcot joint foot and ankle diagnosed based on clinical pictures and plain radiographs. The type II DM patients without charcot joint of foot and ankle who did not suffer from charcot joint belong to the control group. Patients' data and medical conditions (name, age, gender, occupation, residence, smoking habits, use of corticosteroids, long history of diabetes mellitus type II, other diseases such as hyperlipidemia, hypertension, foot and ankle fracture, and peripheral artery disease) were obtained through anamnesis in the Outpatient Installation and Inpatient Installation of RSUP Sanglah and medical record. Diagnosis of charcot joint foot and ankle was obtained from the results of physical examination of according to Eichenholtz Classification and x-ray examination of foot and ankle which was performed at the Radiology Installation of RSUP Sanglah. The inferential analysis was used determine whether the results of this study can be generalized to the general population, using 95% CI and p-value <0.05 was considered as significant. The inferential statistical test used in this study was chi-square. Logistic regression was used to assess several major risk factors with the strongest influence on the incidence of Charcot joint foot and ankle in type II Diabetes Mellitus. Statistical Package for Social Sciences (SPSS) for Windows® version 20 program was used for data processing.

The sample size in this study was determined by consecutive sampling, namely by recording patients according to the inclusion and exclusion criteria until the number of participants according to the requirements of the analysis was met. A comparative case study and analytical control formula was used to calculate the sample size. The inclusion criteria are Patients who are diagnosed with type II DM with charcot joint foot and ankle and patients who are willing to participate in the study with informed consent form. The exclusion criteria are patient with routine use of corticosteroid, no habit and previous history of smoking, patients who refuse to participate in the study, patients with neuritis / neuropathy of the lower extremity due to other causes other than type II DM,

and patients with history of ankle reconstruction surgery.

RESULTS

The descriptive analysis was done to see the distribution of the characteristics of the research subjects (Table 1). Based on the demographic data gathered, male gender dominated both the Type II DM group with Charcot joint foot and ankle and the Type II DM group without Charcot joint foot and ankle, which were 51.9% and 48.1% respectively. From the side of the foot affected, most of the subjects in the Type II DM group with Charcot joint foot and ankle were on the right foot side with 15 people (62.5%). Based on the Eichenholtz classification in the Type II DM group with Charcot joint foot and ankle, the highest number was found at stadium III with 17 people (70.8%) and the lowest at stadium II with 2 people (8.3%). The most common duration of Type II DM in the Type II DM group with Charcot joint foot and ankle was ≥ 10 years with 14 people (58.3%), while in the Type II DM group without Charcot joint foot and ankle, the number of subjects with of duration of type II DM <10 years was 20 people (83.3%) with a standard deviation of both groups 8.42 ± 5.77. The results of the HbA1c examination in both groups showed HbA1c levels of 7% found in 16 people (66.7%) in the case group, while in the control group the HbA1c levels were <7% found in 15 people (62.5%) with a deviation standard 7.88 ± 3.02. The results of the TNF-α examination in the two groups showed the TNF-α levels 1.0 ng/L is the most common result in the case group with 19 people (79.2%), while TNF-α levels <1.0 ng/L in 14 people. (58.3%) in the control group with a standard deviation of 14.67 ± 14.67. The results of the IL-10 examination showed IL-10 levels 255 pg/mL were found in 20 people (83.3%) in the case group. While in the control group, the most common result was IL-10 levels > 255 pg/mL with 13 people (54.2%) with a standard deviation of 177.34 ± 170,34 for both groups.

Table 1. The Distribution of Characteristics of the Research Subjects

Variable	Total (%)		Mean ± Standard Deviation
	Type II DM with Charcot joint foot and ankle	Type II DM without Charcot joint foot and ankle	
Age (years)			54.25 ± 10.373
Sex Male Female	 14 (58.3%) 10 (41.7%)	 13 (54.2%) 11 (45.8%)	
The affected side Right Left	 15 (62.5%) 9 (37.5%)	 0 (0%) 0 (0%)	
Eichenholtz stadium Stadium II Stadium III Stadium IV	 2 (8.3%) 17 (70.8%) 5 (20.8%)	 0 (0%) 0 (0%) 0 (0%)	
Duration of Type II DM < 10 years ≥ 10 years	 10 (41.7%) 14 (58.3%)	 20 (83.3%) 4 (16.7%)	8.42 ± 5.77
HbA1c Level HbA1c ≥ 7% HbA1c <7%	 16 (66.7%) 8 (33.3%)	 9 (37.5%) 15 (62.5%)	7.88 ± 3.02
TNF-α Level TNF-α ≥1,0 ng/L TNF-α <1,0 ng/L	 19 (79.2%) 5 (20.8%)	 10 (41.7%) 14 (58.3%)	14.67 ± 14.67
IL-10 Level IL-10 ≤ 255 pg/mL IL-10 > 255 pg/mL	 20 (83.3%) 4 (16.7%)	 11 (45.8%) 13 (54.2%)	177.34 ± 170.34

The duration of Type II DM ≥10 years and Charcot joint foot and ankle in patients with Type II DM can be seen on Table 2. There is a significant difference (p= 0.003, p< 0.05) between the duration of Type II DM ≥10 years and < 10 years. Further analysis obtained an Odd Ratio (OR) of 7 so that patients with Type II DM ≥10 years had a 7 times higher risk of developing Charcot joint foot and ankle

compared to the population with Type II DM <10 years. Based on the p-value = 0.003 and CI95% = 1.822-26,887, this odd ratio value can be generalized to the general population.

Table 2. The duration of Type II DM ≥10 years and Charcot joint foot and ankle in patients with Type II DM

Variable	Type II DM groups		P	OR (95%CI)
	With Charcot joint foot and ankle	Without Charcot joint foot and ankle		
Duration of Type II DM < 10 years ≥ 10 years	 10 (41.7%) 14 (58.3%)	 20 (83,3%) 4 (16.7%)	0.003	7 (1.822-26.887)

The HbA1c level and Charcot joint foot and ankle in patients with Type II DM can be seen in Table 3. There was a statistically significant difference in risk of Charcot joint foot and ankle (p= 0.043, p < 0.05) between Type II DM patients with HbA1c ≥7% compared to HbA1c < 7%. Further analysis obtained an Odd Ratio (OR) of 3.333 so that patients with higher HbA1c levels (HbA1c levels ≥7%) had a 3.333-fold greater probability of Charcot joint foot and ankle compared to the population with lower HbA1c levels (HbA1c levels <7%). The p-value = 0.043 and 95%CI = (1.020-10.898) means that the odds ratio value obtained can be generalized to the general population.

Table 3. The HbA1c level and Charcot joint foot and ankle in patients with Type II DM

Variable	Type II DM groups		P	OR (95%CI)
	With Charcot joint foot and ankle	Without Charcot joint foot and ankle		
HbA1c Level ≥ 7% < 7%	 16 (66.7%) 8 (33.3%)	 9 (37.5%) 15 (62.5%)	0.043	3.333 (1.020-10.898)

TNF-α levels and Charcot joint foot and ankle in patients with Type II DM can be seen in Table 4. There was a statistically significant difference (p= 0.008, p < 0.05) between TNF-α levels ≥1.0 ng/L compared to TNF-α levels <1.0 ng/L. Further analysis obtained an Odd Ratio (OR) of 5.320 so that the type II DM patients with TNF-α levels ≥1.0 ng/L had 5.320 times the higher probability for Charcot joint foot and ankle compared to the population with TNF-α <1.0 ng/L. With 95%CI= (1.485-19.064) and p-value = 0.008, this odd ratio value can be generalized to the general population.

Table 4. TNF-α levels and Charcot joint foot and ankle in patients with Type II DM

Variable	Type II DM groups		P	OR (95%CI)
	With Charcot joint foot and ankle	Without Charcot joint foot and ankle		
TNF-α Level ≥ 1.0 ng/L < 1.0 ng/L	 19 (79.2%) 5 (20.8%)	 10 (41.7%) 14 (58.3%)	0.008	5.320 (1.485-19.064)

Level of IL-10 and Charcot joint foot and ankle in patients with Type II DM can be seen in Table 5. There was a statistically significant difference (p= 0.007, p < 0.05) between IL-10 levels ≤ 255 pg/mL compared to IL-10 levels >255 pg/mL. Further analysis obtained an Odd Ratio (OR) of 5.909 so that type II DM patients with IL-10 levels ≤255 pg/mL had a 5.909-fold higher possibility of Charcot joint foot and ankle compared to the population with IL-10 ≤255 pg/mL. With 95%CI = 1.546-22.580 and p-value = 0.007, the odds ratio value can be generalized to the general population.

Table 5. Level of IL-10 and Charcot joint foot and ankle in patients with Type II DM

Variable	Type II DM groups		P	OR (95%CI)
	With Charcot joint foot and ankle	Without Charcot joint foot and ankle		
IL-10 Levels ≤ 255 pg/mL > 255 pg/mL	 20 (83.3%) 4 (16.7%)	 11 (45.8%) 13 (54.2%)	0.007	5.909 (1.546- 22.580)

Based on the multivariate analysis, it can be seen in Table 6 that the strongest risk factors of Charcot joint foot and ankle was the duration of Type II DM ≥ 10 years (RR=9,767), while the weakest risk factor was IL-10 levels≤255pg/mL(RR-0,149).

Table 6. Risk factors of Charcot joint foot and ankle in type II DM patients

Risk Factors	Exp(B)	95% CI for Exp(B)	
		Lower	Upper
Duration of Type II DM tipe ≥ 10 tahun	9.767	1.657	57.557
HbA1c ≥ 7%	2.842	0.607	13.310
TNF-α ≥ 1,0 ng/L	3.751	0.812	17.337
IL-10 ≤ 255 pg/mL	0.149	0.24	0.904

DISCUSSION

This study showed that there are multiple risk factors in the development of Charcot joint foot and ankle, which are the duration of type II DM ≥ 10 years, HbA1c ≥ 7%, TNF- ≥ 1.0 ng/L, and IL-10 ≤ 255 pg/mL. A previous cross-sectional study by Wanzou et al.[8] evaluated the factors associated with the incidence of Charcot joint foot and ankle in patients with type II DM at a referral hospital in Uganda. It was found that 43% of all patients had a duration of type II diabetes >10 years. Meanwhile, in another case-control study by Fauzi et al.[9] in Malaysia, it was observed that from 48 cases of type II DM patients with Charcot joint, it showed that duration of type II DM had a significant relationship to the occurrence of Charcot joint, with the majority of patients (89.4%) had duration of type II DM ≥10 years. It was concluded that duration of type II DM ≥10 years increases the risk of Charcot joint foot and ankle up to 6.7 times compared to the group with a duration of type II DM < 10 years. In another study conducted by Stuck et al.[5], it was also found that patients with type II DM duration > 6 years had Charcot joint foot and ankle at a rate twice as high as those with type II DM 6 years.

In this study, it was shown that HbA1c ≥7% was significantly associated with the incidence of Charcot joint foot and ankle. This result is similar to a study by Younis et al.[9], which stated that there was a significant relationship between the occurrence of the Charcot joint with HbA1c levels ≥6.6% with an increase in the risk of almost 4.3 times higher compared to the HbA1c level of <6.6%. However, another study by Dardari et al.[70] concluded that aggressively lowered HbA1c levels in patients with a history of uncontrolled diabetes significantly increased the onset of Charcot joint foot and ankle. This aggressive reduce in HbA1c levels in uncontrolled diabetic patients will cause activation of inflammatory phenomena through the OPG pathway, which triggers the development of Charcot joint foot and ankle.

It was also found that TNF-α levels ≥1.0 ng/L plays a significant role in the development of Charcot joint foot and ankle. TNF-α is a pro-inflammatory cytokine that has an important role in the expression of the RANKL gene, causing a local process of osteolysis and disrupting the integrity of bone tissue so that patients with diabetes have a high risk of fracture, deformity, and ulceration.[68] A study conducted by Petrova et al.31 reported that TNF-α in the group of controlled diabetes patients without the Charcot joint were significantly higher than those with Charcot joint. Meanwhile, the TNF-α levels in the DM patients with Charcot joint were 1.3 ng/l higher during the fourth month follow-up compared to the controlled diabetes group and the healthy patient group. But there was a different result in a study conducted by Folestad et al.[23] which stated that TNF-α levels increase when compared between controls of DM patients with healthy people. TNF- α levels are below or equal to the comparison of DM with CNA with healthy people, while the ratio of IL-1RA / IL-1β is continuously higher in CNA patients. IL-6, TNF-α, and IL-1RA started to increase one week after offloading to peak after 4 months before slowly decreasing.

IL 10 < 255 pg/mL is also found to be a risk factor for Charcot joint foot and ankle. IL-10 acts as an important immunoregulator, by reducing the

production of proinflammatory cytokines and reactive oxygen species that cause cell damage. IL-10 is known to be produced by T helper 2 cells, B cells, mast cells, and granulocytes.[35] Until now, there are still few studies that explain the relationship between IL-10 level and type II DM and Charcot joint foot and ankle, thus, further investigations are needed to know about the balance between anti-inflammatory and pro-inflammatory cytokines since high inflammation is not affected by the IL-10 levels. Bio molecularly, low levels of IL-10 will increase proinflammatory cytokines such as TNF- α, IL-1β, and IL-6 which results in high local inflammation, maturation, and proliferation of osteoclasts through the RANKL pathway, which can lead to Charcot joint foot and ankle.[21,69] A descriptive study conducted by Johnson-Lynn et al.[21] from 66 articles stated that in CNA severe chronic inflammation occurs, thereby increasing the production of pro-inflammatory cytokines such as TNF-α, IL1β, and IL6. At the same time, even at lower levels, there was increased expression of anti-inflammatory cytokines such as IL-4 and IL-10.[70]

CONCLUSION

In conclusion, there were multiple significant risk factors in the development of Charcot joint foot and ankle in patients with type 2 DM. It was found that duration of type II DM ≥ 10 years was the strongest risk factors compared to other risk factors evaluated in this study. The low level of IL-10 was found to be the weakest risk factor, as concluded in other studies assessing IL-10 level in Charcot joint foot and ankle patients with type 2 DM.

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Conflict of Interest: The author states that there is no conflict of interest related to the material discussed in the manuscript.

Ethical Approval: The research protocol for Ethical Clearance from the Research Ethics Commission at the Faculty of Medicine, UNUD / Sanglah Hospital Denpasar will be submitted before the research is carried out. Subjects who met the study criteria were given an explanation of the purpose of the study and were asked to fill out written informed consent. Researchers have also attached a secondary data collection permit in the form of a medical record at Sanglah Hospital Denpasar

Authors' Contribution: Indra Rukmana Tri Pratistha is responsible for finding research samples, implementing actions, and analyzing data, and reporting on research results. Ketut Siki Kawiyana, IGN Wien Aryana, I Gede Eka Wiratnaya, and KG Mulyadi Ridia were responsible for the research design concept and the supervisor in this study.

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