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ORIGINAL RESEARCH

A Pilot Study of Diabetes Distress with Insulin Growth Factor-I, Insulin-Like Growth Factor Binding Protein-3, and HbA1c of Diabetic Patients

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Abstract

Background: Diabetes distress refers to the emotional and psychological burden experienced by individuals in managing their condition, which can influence physiological outcomes and overall well-being. However, the relationship between HbA1c, insulin growth factor-I (IGF-I), and insulin-like growth factor binding protein-3 (IGFBP-3) with diabetes distress in diabetic patients remains elusive.

Purpose: The objective of this study was to evaluate the association of IGF-I, IGFBP-3, and HbA1c with diabetes distress in diabetic patients.

Methods: A cross-sectional design with purposive sampling was used to recruit subjects from the public health center in Kendari City, Southeast Sulawesi, Indonesia, from May to November 2021. A total of 30 diabetic patients were recruited for the study. Distress data were collected using the Indonesian version of the Diabetes Distress Scale (DDS) questionnaire. HbA1c levels were measured using High-Performance Liquid Chromatography (HPLC). Serum levels of IGF-I and IGFBP-3 were measured using the ELISA (Enzyme-Linked Immunosorbent Assay) kit method. The data were analyzed using regression analysis.

Results: Most respondents had moderate distress, with a DDS score of 53.4%, a high IGF-I level of 76.7%, and a low IGFBP-3 level of 76.7%. As many as 60% of respondents had an HbA1c level above 6.4%. IGF-I (ρ-value=0.024) and IGFBP-3 levels (ρ-value=0.042) showed a significant correlation with diabetes distress. However, HbA1c levels did not significantly correlate with diabetes distress (ρ-value=0.155).

Conclusion: IGF-I and IGFBP-3 levels were associated with diabetes distress, but HbA1c was not. Patients with higher distress were found to have elevated serum levels of IGF-I and IGFBP-3. Future research should focus on stress management strategies that support efforts to prevent disease and complications associated with diabetes mellitus.

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1. Introduction

Diabetes has become a significant health concern. Worldwide today, nearly half a billion people live with diabetes. In 2019, the IDF Diabetes Atlas reported that an estimated 463 million people had diabetes. This number is estimated to reach 578 million in 2030 and 700 million in 2045. In Southeast Asia, 88 million people have diabetes, while Indonesia was ranked 7th in the world, with 10.7 million cases (International Diabetes Federation, 2019).

Diabetic distress is a psychological burden that lasts a lifetime. It occurs due to stressful conditions and is related to neuroendocrine responses through the hypothalamic-pituitary-

adrenal axis (Aguirre et al., 2016; Ramkisson, 2017; Stoop et al., 2019). The emotional stress that results from living with diabetes occurs due to the relentless burden of disease and the risk of long-term complications (Skinner et al., 2020). Diabetes distress can worsen health if not properly managed (American Diabetes Association, 2020). Additionally, diabetes distress can disrupt the quality of life, metabolism, and homeostasis of the human body (Önal et al., 2014; Young-Hyman et al., 2016).

High blood glucose levels can trigger diabetes distress (Alves-Bezerra & Cohen, 2019). One of the markers that can detect the average increase in a person's blood glucose is the HbA1c test. Biochemically, HbA1c is formed by a nonenzymatic reaction in which glucose attaches to the amino-terminal valine of one or both beta chains of hemoglobin A (Sandler & McDonnell, 2022). HbA1c values are used for average glycemic control over the past 2-3 months (Schnell et al., 2017).

As much as 99% of circulating IGF-I is bound to IGF-binding proteins (IGFBPs), including IGFBP-3 (Wennberg et al., 2018). IGF-1 is a hormone that manages the effects of growth hormone (GH) in the human body, and IGFBP-3 is the primary carrier of somatomedin C (also called insulin-like growth factor-1, or IGF-1) in the body. IGF-I levels in the nucleus play a role in glucose homeostasis, lowering glucose levels and increasing insulin sensitivity (Klop et al., 2013). Changes in circulating IGF-I and its binding proteins cause impaired glucose tolerance (Kristaningrum et al., 2021). Furthermore, IGFBP-3 forms a complex with IGF-I (Ranke, 2015). IGFBP-3 functions as a guard to maintain IGF-I levels in the nucleus. IGFBP-3 levels are elevated in patients with diabetes mellitus (DM) (Hu et al., 2020).

There have been reports on the relationship between HbA1C, IGF-I, and IGFBP-3 with elevated blood sugar levels in DM patients (Abdlwhab et al., 2024; Fraenkel & Lazurova, 2023; Kasprzak, 2021; S. Y. Kim et al., 2021; Vasilkova et al., 2021). Liu and Wang found that serum levels of IGF-I and IGFBP-3 were significantly higher in patients with type 2 DM. In contrast, the serum levels of IGF-I and IGFBP-3 were related to HbA1c, and IGFBP-3 levels also correlated with cholesterol (Liu & Wang, 2024). Furthermore, it was also reported that IGF-I levels were significantly low in patients with type 1 DM, while HbA1c had a negative relationship with DM (Botros et al., 2020). The IGF-I – IGBP-3 axis plays a role in regulating glucose balance and metabolism. It also plays a role in the mechanism of DM pathogenesis (Clemmons, 2018). However, the adaptive mechanism of diabetes distress to serum IGFBP-3 changes in diabetic patients is still rarely studied. These serum changes reduce the action of IGF-1 (Wei et al., 2023).

Treatment of DM begins with nutritional therapy and physical exercise. If blood sugar levels have not reached the target, this is followed by the administration of oral hypoglycemic drugs or insulin injections. Therefore, controlling and monitoring blood sugar levels in DM patients with distress is necessary. High sugar levels can contribute to diabetic distress, which is triggered by worries, anxiety, fear, and concerns related to treatment. More specific blood sugar examinations, including HbA1c levels, IGF-I, and IGFBP-3, are essential for making informed nursing care and treatment decisions. These biomarkers are important for monitoring long-term glycemic control in diabetes management. However, the relationship between HbA1c, IGF-I, and IGFBP-3 with diabetes distress in diabetic patients remains elusive. Therefore, this study was conducted to evaluate the association of IGF-I, IGFBP-3, and HbA1c with diabetes distress in DM patients.

2. Methods

2.1. Research design

A cross-sectional design was used to assess the correlation between IGF-I, IGFBP-3, and HbA1c levels with diabetes distress. It is an observational study that analyzes data at a single point in time. The design of these studies is usually inexpensive and easy to perform (Wang & Cheng, 2020). It enables researchers to gather information on the prevalence of outcomes or exposures, as well as the relationship between exposures and outcomes (Setia, 2016).

2.2. Setting and samples

A total of 30 respondents were involved in this study. The sample size was calculated using G*Power software (α=0.05; ß=0.90; f^2=0.5). Purposive sampling was used to recruit subjects from the Public Health Centre (PHC) in Kendari City, Southeast Sulawesi, Indonesia. Inclusion criteria included DM patients diagnosed by a medical doctor, aged 20-79 years, who could communicate well and were willing to take their blood for examination in the laboratory. Patients who refused were excluded from this study. This study was conducted from May to November

2021. According to the data obtained, in the PHC where this study took place, there was a decrease in patient visits, including those with diabetes, due to the COVID-19 pandemic. This pandemic caused fear among patients, making them reluctant to visit the PHC. In this study, 37 people with diabetes were initially recruited; however, some patients declined to participate due to fears associated with the COVID-19 pandemic. During the study, 7 respondents dropped out due to fear of being exposed to COVID-19 during blood sample collection.

2.3. Measurement and data collection

Data collection in this study was conducted during the COVID-19 pandemic following protocols established by the government. After obtaining research permits, the researchers coordinated with the PHC to recruit participants. DM patients who were potential participants received information about the study procedures, and their consent was obtained. The data collection procedure involved collecting demographic data, completing questionnaires, and conducting blood and serum tests. Researchers were assisted by research assistants with health backgrounds and experience in conducting research. Data collection included the examination of HbA1c levels, serum IGFBP-3 levels, serum IGF-I, and the DDS17 Bahasa Indonesia questionnaire, all conducted according to standard protocols by healthcare workers. Participants provided demographic data (gender, age, occupation, education, and duration of diabetes) and completed the DDS17 Bahasa Indonesia.

Distress data were collected using the Indonesian version of the diabetes distress scale (DDS). The DDS was developed by William H. Polonsky from the Problem Areas in Diabetes (PAID) instrument and is widely recommended for assessing distress in patients with diabetes (Arifin et al., 2017; Polonsky et al., 2005). The DDS17 Bahasa Indonesia version has demonstrated a more precise and cross-culturally consistent factor structure (Arifin et al., 2017; Polonsky et al., 2005). The DDS consists of 17 items measuring patients' feelings in four domains. Each item is rated on a scale from 1 (not a problem) to 6 (a very serious problem), producing a total score ranging from 17 (not a problem) to 102 (very serious problem). The DDS17 Bahasa Indonesia version has been psychometrically validated, demonstrating a good factor structure and internal consistency for assessing distress in Indonesian diabetes outpatients. An overall score of <2.0 indicates little or no distress, 2.0 – 2.9 indicates moderate distress, and ≥3.0 indicates higher distress (Arifin et al., 2017, 2019). The instrument demonstrated high internal reliability, with Cronbach's alpha values ranging from 0.78 to 0.83. The validity was supported by factor analysis using maximum likelihood and Promax rotation, revealing inter-factor correlations ranging from 0.40 to 0.67.

HbA1c levels were measured using High-Performance Liquid Chromatography (HPLC). The HbA1c test used 3 cc of blood, collected by inserting a needle into a vein and placing it in an EDTA vacutainer. The procedure began with the application of 0.13% latex, buffer, stabilizer, anti-human HbA1c reagent, and a photometer (cuvette holder) set to 37°C. Samples were mixed and incubated for 5 minutes, with results available within 2-3 minutes.

A total of 1 mL of serum was collected in tubes and stored at −70°C. The IGF-I and IGFBP-3 levels were assessed from a 5-cc blood sample. After clotting for 2 hours at room temperature or overnight at 4°C, samples were centrifuged at 1000 × g for 20 minutes in a serum separator tube. Analyses were conducted in the laboratory of the Faculty of Pharmacy, Universitas Halu Oleo.

IGF-I and IGFBP-3 levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit. The procedure began with the preparation of standards and reagents. Then, 50 µL of standards and serum samples were added to each well, followed by 50 µL of working biotin-conjugate antigen. Plates were incubated for 1 hour at 37°C and then washed three times. Next, 100 µL of working streptavidin-HRP was added and incubated for 30 minutes at 37 °C, followed by five washes. Then, 90 µL of substrate solution was added and incubated for 15-20 minutes at 37°C in the dark. Afterward, 50 µL of stop solution was added. Last, optical density was measured within 5 minutes at 450 nm, with the correction wavelength set at 570 nm or 630 nm.

Data were analyzed using regression analysis. The IGF-1 to IGFBP-3 was also calculated and categorized using quintile cut points (Duggan et al., 2014). For IGF-I, scores below 53.5 ng/mL were categorized as low, 53.5 – 220 ng/mL as normal, and above 220 ng/mL as excessive.

2.4. Data analysis

For univariate analysis in this study, descriptive statistics were used to describe categorical data (respondents' characteristics), while means and standard deviations were used for numerical

data. Data analysis was performed using the Pearson correlation test to examine the correlation between serum IGF-1, IGFBP-3, and HbA1c levels with diabetic distress. A p-value of <0.05 was considered statistically significant. Statistical analysis was conducted using IBM SPSS for Windows Version 24 (IBM Corp, Armonk, NY).

2.5. Ethical considerations

This study was approved by the Southeast Sulawesi IAKMI Ethics Commission (Number 51/KEPK-IAKMI/V/2020). Prior to data collection, the researchers informed prospective participants about the study's objectives, benefits, procedures, and potential risks. Participation was voluntary. All participants signed an informed consent form prepared by the researchers. Confidentiality of participant information was strictly maintained throughout the study.

3. Results

The results showed that the study included 30 participants (Table 1). Most of them were female (63.3%), high school graduates (46.7%), housewives (60%), 51-60 years of age (33,3%), and experienced medium distress (53,4). They had DM for less than five years (76.7%), high IGF-I level (76.7%), HbA1c level with diabetes (60%), and low IGFBP-3 level (76.7%).

Table 1. Sociodemographic characteristics of the study participants (n=30)

Characteristics	f	%
Gender		
Male	11	36.7
Female	19	63.3
Age (Years)		
Mean (SD)	56.1 (10.743)	
31-40	1	3.3
41-50	8	26.7
51-60	10	33.3
61-70	9	30
71-80	2	6.7
Employment		
Retired	4	13.3
Housewives	18	60
Civil Servants	3	10
Self-employment	3	10
Not Working	2	6.7
Education		
Elementary	8	26.7
Junior School	3	10
High School	14	46.7
College	5	16.7
Diabetes Duration (Years)		
< 5	7	23.3
5 – 10	15	50
> 10	8	26.7
Diabetes Distress		
Mean (SD)	2.571 (0.50027)	
Little or no DD	7	23.3
Moderate DD	16	53.4
High DD	7	23.3
HbA1c		
Mean (SD)	7.587 (3.0441)	
Normal	9	30
Pre-Diabetes	3	10
Diabetes	18	60
IGF-I Level		
Mean (SD)	229.847 (19.0169)	
Low	0	0
Normal	7	23.3
Excessive	23	76.7
IGFBP-3 Level		
Mean (SD)	11851.948 (17734.587)	
Low	0	0
Normal	7	23.3
Excessive	23	76.7

Table 2 illustrates the relationship between IGF-I levels and IGFBP-3 in relation to diabetes distress (ρ-value = 0.024 and ρ-value = 0.042, respectively). Furthermore, there is no relationship between HbA1c and diabetes distress (ρ-value = 0.155). The highest stress level was experienced by diabetes patients with IGF-I levels more than normal, as many as 7 people (23.3%). Those who experienced the most stress were diabetes patients who had excessive serum levels with moderate stress levels of as many as 12 people (40%). The highest stress was experienced by diabetes patients with serum IGFBP-3 levels below normal, affecting as many as 6 people (20%).

Table 2. Relationship of IGF-I, IGFBP-3, and HbA1c levels with diabetes distress (DD) (n=30)

Variable	Diabetes Distress			*ρ*-value
	Little or no DD (<2.0)	Moderate DD (2.0 – 2.9)	High DD (3.0 ≥)	
IGF-I Serum level				
Normal	2 (6.7)	5 (16.7)	0 (0)	0.024
Excessive	4 (13.3)	12 (40)	7 (23.3)	
IGFBP-3 Serum level				
Low	2 (6.7)	15 (50)	6 (20)	
Normal	1 (3.3)	0 (0)	1 (3.3)	0.042
Excessive	3 (10)	2 (6.7)	0 (0)	
HbA1c level				
Normal (< 5.6%)	0 (0)	2 (6.7)	4 (13.3)	
Pre-Diabetes (5.7-6.4)	6 (20)	1 (0)	10 (33.3)	0.155
Diabetes (≥ 6.5)	3 (10)	0 (0)	4 (13.3)	

4. Discussion

This study investigates the relationship between serum levels of IGF-I, IGFBP-3, and HbA1c with diabetes distress in people with DM. It found that moderate levels of diabetes distress mainly occur in diabetic patients. This study also shows that serum IGF-I and HbA1c levels tend to be high, whereas serum IGFBP-3 levels are low. Furthermore, serum levels of IGF-I and IGFBP-3 are associated with diabetes distress, whereas HbA1c levels show no relationship with diabetes distress.

In this study, of the 30 DM patients, most (53.4%) experienced moderate levels of distress. Similar research has been conducted by Aljuaid et al., who reported that 25% of participants had moderate diabetic distress, and 54% had moderate emotional distress. Diabetes distress with a moderate scale from the DDS-17 score is commonly caused by pressure related to healthcare providers and treatment regimens after interpersonal and emotional stressors (Aljuaid et al., 2018). Furthermore, AlOtaibi et al. also reported noted a 25.6% prevalence of moderate diabetic distress. This shows that depression among elderly diabetic patients is a significant concern. Diabetic patients are more likely to seek care in inpatient facilities. Furthermore, the older the patient, the more common the complications experienced, the lower the physical mobility, and the greater the tendency to consume more drugs (AlOtaibi et al., 2021). Meanwhile, Cinedu and Foluso stated that patients with high-category diabetes distress had a lower quality of life (Chinedu & Foluso, 2023).

Stress has a negative impact on health and is a significant barrier to effective diabetes management. These stress-induced changes make it difficult for patients to change their lifestyles and comply with the required therapy (Hilliard et al., 2016; Jeong & Reifsnider, 2018). The pathophysiological relationship between stress and diabetes is a direct neuroendocrine effect (Harris et al., 2017). Diabetes distress and depressive symptoms are considered contributors to poor glycemic control (Jeong & Reifsnider, 2018). Previous studies reported that young adults with diabetes in China had severe diabetes disorders (Hu et al., 2020). In Iran, 35% of 185 diabetes patients experienced stress (Baradaran et al., 2013), while in South East Nigeria, among 110 patients, type 1 diabetes sufferers were more likely to experience diabetes distress than those with type 2 diabetes (Young et al., 2020). Stress stimulates the production of hormones such as epinephrine and cortisol (Thau et al., 2023). Epinephrine triggers gluconeogenesis in the liver, whereas cortisol acts in opposition to insulin (Kim & Park, 2017; Thau et al., 2023). Severe stress in diabetics leads to increased cortisol production, thereby reducing the body's sensitivity to insulin (Pratiwi et al., 2014; Zamani-Alavijeh et al., 2018). Likewise, moderate diabetic distress also increases the secretion of glucocorticoids (cortisol) and catecholamines (epinephrine)

(Vedantam et al., 2022). The physiological responses associated with diabetic distress affect the functioning of the pituitary-hypothalamic axis and impact endocrine functions, such as increased cortisol levels (Joseph & Golden, 2018). Elevated cortisol affects insulin secretion, stimulates gluconeogenesis, and inhibits glucose absorption, leading to increased blood glucose and cholesterol levels (Hatting et al., 2018). High glucose levels are linked to the neuroendocrine system through the Hypothalamic-Pituitary-Adrenal (HPA) axis, the central stress response system in humans (Zamani-Alavijeh et al., 2018).

The current study showed a relationship between serum IGF-I levels and diabetes distress. Patients with high stress had IGF-I levels above normal (Oguni et al., 2024). Indirectly, IGF-I provides biological effects on diabetic distress. When insulin resistance occurs, the body cannot uptake glucose efficiently and also fails to suppress hepatic glucose output (Zhao et al., 2023). Ultimately, the buildup of glucose in the blood leads to the onset of diabetes (Sapra & Bhandari, 2023). Living with diabetes requires proper management of the disease condition. If it is not managed correctly, it may trigger emotional responses or diabetes distress, including anxiety, guilt, and worry (Kalra et al., 2018).

The role of IGF-I in controlling glucose homeostasis has been previously reported. IGF-I regulates glucose and lipid metabolism (Oguni et al., 2024). Similä et al. suggested that the IGF axis plays a critical role in maintaining normal glucose regulation (Similä et al., 2019). IGF circulates in plasma by binding to IGFBPs. Several studies have examined the relationship between IGF and diabetes. NeamŢu et al. found that serum levels of IGF-I and IGBP-3 were increased in patients with diabetes (NeamŢu et al., 2017). The IGF-I axis helps regulate glucose metabolism and maintain normal glucose and lipid balance (Aneke-Nash et al., 2015; Clemmons, 2012; Similä et al., 2019). Furthermore, IGF-I is also known to play an essential role in the development of diabetic disease (Biadgo et al., 2020). In diabetes, circulating IGF-I plays a vital role in glucose regulation, as it is positively correlated with insulin resistance and glucose metabolism (Kim et al., 2021).

A relationship exists between serum IGFBP-3 levels and diabetes distress. Patients with lower IGFBP-3 levels tend to experience higher stress. Kim et al. (2021) reported that serum IGFBP-3 levels were positively correlated with fasting plasma glucose levels and HbA1c. The IGF-I-IGFBP-3 axis, specifically IGFBP-3, plays a crucial role in the pathogenesis of glucose intolerance and metabolic regulation, particularly in patients with diabetes (Kim et al., 2021). Furthermore, Vasilkova et al. also reported that IGFBP-3 tends to decrease in diabetic patients while it helps regulate glucose homeostasis (Vasilkova et al., 2021). Aneke-Nash et al. also reported that IGFBP-3 is strongly associated with a high risk of diabetes in women (Aneke-Nash et al., 2015). Drogan also reported that IGFBP-3 was positively associated with the risk of diabetes (Drogan et al., 2016). However, Similä et al. found no relationship between IGFBP-3 and diabetes risk (Similä et al., 2019). It is assumed that glucose uptake is not optimal in patients with low levels of IGFBP-3. Diabetic distress increases blood sugar levels by triggering gluconeogenesis in the liver, causing the release of excessive glucose into the bloodstream. Prolonged diabetic distress can impair the pancreas' ability to regulate insulin production. This is contrary to the mechanism of action of IGFBP-3. In the plasma, IGFBP-3 binds to IGF-I to facilitate glucose uptake. Suboptimal insulin production reduces the effectiveness of IGBP-3 in supporting glucose uptake.

In this study, no relationship was found between HbA1c and diabetes distress. However, some previous studies have reported different findings. Wibowo et al. found a significant positive correlation between diabetes distress and HbA1c (Wibowo et al., 2022). Similarly, Batais et al. (2021) and Elotla et al. (2022) reported a significant association between HbA1c levels and diabetes distress. The correlation between diabetes distress and HbA1c was dominant in the range of 0.15 to 0.26 (Wibowo et al., 2022). Pankiv and Yuzvenko, in 2023, reported that diabetes distress in adults is associated with elevated HbA1c levels, and this relationship is more potent than that in diabetes self-care (Pankiv & Yuzvenko, 2023). Chronic stress is closely associated with living with diabetes, including its impact on HbA1c levels (Hilliard et al., 2016). HbA1c is a biomarker that reflects glucose tolerance and helps regulate blood glucose levels in diabetes (Gedikli et al., 2022). It is widely used as a standard indicator of glycemic control to estimate average glucose levels over the last 2 to 3 months (Jeong & Reifsnider, 2018). Additionally, it is used to predict the risk of potential complications (Gedikli et al., 2022). HbA1c levels vary among DM patients, depending on their diabetes history (Sherwani et al., 2016).

5. Implications and limitations

This research may serve as an evidence-based practice for nurses who provide care to patients with diabetes distress by analyzing their diabetes history. Examination of IGF-I and IGFBP-3 serum levels can help assess the presence of stress in patients. Thus, follow-up plans for managing diabetes stress are necessary, with the hope that stress levels can be reduced or avoided. In integrating the diabetes healthcare system, nurses can apply stress management strategies to prevent the development of pre-diabetes and diabetes complications. This proactive approach not only supports the health and well-being of people with diabetes but also reduces the long-term burden on the healthcare system.

This study has limitations. During data collection, some prospective participants refused to participate due to fear of blood sampling in the post-COVID-19 pandemic period. Despite receiving thorough explanations, some believed the study was still related to the COVID-19 pandemic activities. This affected the suboptimal recruitment of participants.

6. Conclusion

IGF-I and IGFBP-3 levels were found to be associated with diabetes distress. Patients with high stress had serum IGF-I levels above normal. Moreover, lower IGFBP-3 levels were linked to higher levels of stress. On the other hand, HbA1c levels did not show a significant correlation with diabetes distress. Therefore, it is necessary to implement stress management strategies in the community to prevent the risk of pre-diabetes and the development of diabetes complications. Efforts to implement these intervention strategies should be developed in a timely manner. Future studies should consider larger and more varied populations to validate the link between diabetes distress, IGF-I, and IGFBP-3. To investigate causal relationships and the potential effects of stress management interventions on these biomarkers, longitudinal research is also recommended.

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Author contribution

TT, DI: Conceptualization, writing the original draft, data collection, data analysis, editing, review, and approval of the manuscript.
SS, AMI: Conceptualization, supervision, review, and approval of the manuscript.
SP: literature review, editing, and review and approval of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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