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International Journal of Diabetes & its Complications

Case Report

Management of Fetal Mesenchymal Hamartoma of the Liver: A Case Report

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Received: 2025 Sep 04 **Accepted:** 2025 Oct 06 **Published:** 2025 Oct 13

Abstract

Introduction: *Hepatic mesenchymal hamartomas are rare benign tumours. Although most cases are discovered after birth, a few antenatal diagnoses have been reported in the literature.*

Case Presentation: *This is an 8-month-old girl with a prenatal diagnosis of a non-vascular an echogenic intra-abdominal mass, 30 mm in size, without septum.*
*After birth, a CT scan showed an exophytic cystic mass of the left liver in segments 2, 3 and 4. It measured 83*37*84 mm. It was next to the liver's left portal branch and away from the hepatic veins. Tumour markers were negative.*
The patient underwent surgery at 8-month-old via a right subcutaneous incision and was found to have a thin-walled cystic mass. This mass was exophytic in relation with segments II and III, measuring 8cm with a cleavage plane, and the entire mass was resected.

Conclusion: *Mesenchymal hamartoma is a rare benign pathology that can be diagnosed antenatally. Complete resection is recommended with a favorable outcome.*

Keywords: Mesenchymal hamartoma, Liver, Fetus, Case report.

1. Introduction

Hepatic mesenchymal hamartomas are rare benign tumors of the liver. They are defined as a focal proliferation of mature normal cells and native stroma that are epithelium-free, well circumscribed, and remote from the bile ducts. They typically manifest in early childhood, with patients aged between 1 month and 5 years [1]. Only a handful of cases have been identified prenatally, with ultrasound findings exhibiting considerable variability [2].

Complete resection is the recommended therapeutic approach, with a favorable outcome [2]. We report here a case of prenatally diagnosed hepatic mesenchymal hamartoma that was successfully treated.

1.1. Aim

A thorough understanding of the natural history of these tumors and skillful surgical treatment are indispensable elements of care.

2. Case Report

This is an 8-month-old girl with a prenatal diagnosis of a non-vascular anechogenic intra-abdominal mass, 30 mm in size, without septum, discovered during the third-trimester ultrasound. She was born at term by caesarean section due to macrosomia and gestational diabetes. The infant demonstrated effective adaptation to life outside. No palpable mass on clinical examination was found.

Abdominal ultrasound revealed the presence of a cystic mass in anterior of the left hepatic lobe with transsonic content, without clean wall or tissue component, with cloisons, some of which are thickened, measuring 79*40*70mm (figure1).

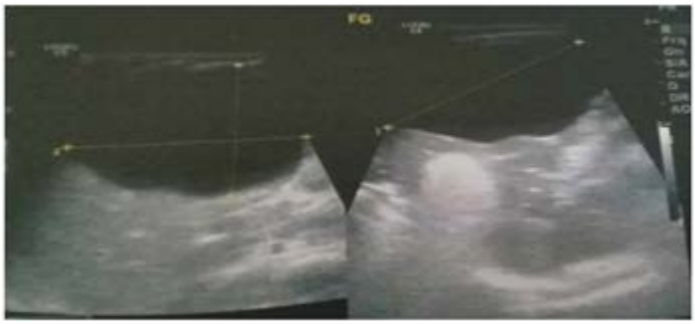

Figure 1: An Abdominal Ultrasound Showed Cystic Mass in Front of the Left Hepatic Lobe with Transsonic Content

A Computed tomography (CT) scan showed an exophytic cystic mass of the left liver in segments 2, 3 and 4. It measured 83*37*84 mm (figure2). It was next to the liver's left portal branch and away from the hepatic veins. On a clinical X-ray, the left liver's mesenchymatous hamartoma appears.

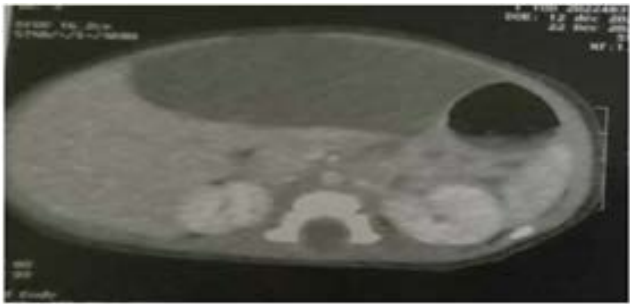

Figure 2: CT Scan of the Abdomen Showed

An exophytic cystic mass of the left liver. Tumour markers were negative. And she has since been lost to follow-up. After 7 months, she returned for a follow-up consultation. There were no identifiable functional signs. Clinical examination revealed no abnormalities.

The radiological examination by ultrasound and abdominal CT scans revealed the same findings as those observed at birth. The patient underwent surgery at 8-month-old via a right subcutaneous incision and was found to have a thin-walled cystic mass with translucent fluid content that was not infected on aspiration. This mass was exophytic in relation with segments II and III, measuring 8cm with a cleavage plane, and the entire mass was resected (figure3: A and B).

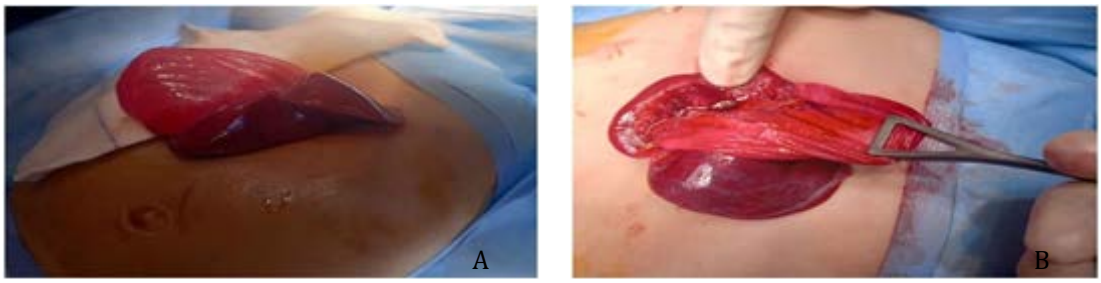

Figure 3: A) B) Intraoperative Photography: Hepatic Mesenchymal Hamartomas.

Pathological examination confirmed the diagnosis of mesenchymal hamartoma.
After one year on follow-up, ultrasound revealed a normal liver with no residual or recurrent tumour.

3. Discussion

Mesenchymal hamartomas were first described in the literature in 1903 by Mares [2]. Initially, these lesions were variously referred to as hepatic lymphangiomas and cavernous lymphangiomatoid tumors. They were subsequently grouped together under the term "mesenchymal hamartoma." These rare benign hepatic tumors that represent 5-8% of primary hepatic tumors [3]. They are the most frequent hepatic tumors in children after hemangiomas [4].

Some author has suggested that it is an anomaly of connective tissue development during fetal life, rather than a true neoplasm [5,6]. They also showed that this pathology could be the consequence of biliary obstruction, ischemia or disordered hyperplasia.

Kapur identified genetic alterations in mesenchymal hamartomas, including androgenetic-biparental mosaicism (ABM) and chromosomal rearrangements, which activate

the chromosome 19q microRNA cluster (C19MC) [6]. A few cases of antenatal diagnosis have been described in the literature (approximately 25 cases) [4].

It may manifest as a cyst or solid mass at antenatal ultrasound. In general, fetal liver hamartomas are mostly avascular lesions on Doppler [1]. While histologically benign, it can cause heart failure due to arteriovenous shunting, as well as compression of the inferior vena cava and umbilical vein [1]. It is important to be careful when doing ultrasounds during pregnancy, especially if the mother's alpha-fetoprotein levels are high as not to break up. Some factors were associated with a poor outcome: early onset, tumor size, rapid growth rate, the presence of hydrops, and compression of arteries by hydramnios [1,5,7]. Liver hamartomas are usually not associated with any abnormality. However, they can be linked to other conditions, including heart disease, intestinal problems, and kidney disease [8-10].

In regard to the mode of delivery, a cesarean delivery is not recommended unless there is a large tumor or fetal distress [1]. After birth, the smallest hamartomas are usually without symptoms. For larger tumors, the most common signs are a swelling in the abdomen and a noticeable mass.

The tumor can make the aFP levels in the blood higher, but they are usually normal. Sometimes the Gamma-glutamyl Transferase (GGT) levels are higher [11].

Given that ultrasound is the preferred initial assessment modality for children, findings can range from small cyst to large septate cyst, with varying degrees of associated echogenic solid tissue. On color Doppler, hepatic mesenchymal hamartomas are typically avascular or have low blood flow.

Abdominal computed tomography (CT) scan showed a multiloculated cystic tumor with a variable amount of solid tissue. Cysts are frequently septated. This multi-cystic configuration is commonly referred to as the “Swiss cheese appearance”.

CT scan is an effective method for investigating the extent of the lesion and its relationship to other organs.

MRI can show the different parts of MHL and how they fit into the tissue around them. The MRI appearance of MHL depends on the protein content of the fluid and the presence of stromal elements [12].

Although some authors have proposed fetal aspiration [13,14]. The results have been unsatisfactory. Thus, prenatal treatment is only a temporary decompression.

After birth, Non-operative management has been suggested in literature given that spontaneous regression of these lesions has been documented [8]. However, complete surgical excision is the only curative option to avoid the risk of recurrence and malignant transformation [2,8].

At section, there are multiple cysts containing a gelatinous serous fluid, but never bile. The composition of this fluid is similar to that of plasma, apart from a lower concentration of protein, cholesterol and glucose [15].

Although the prognosis after resection is excellent, clinical and radiological follow-up is recommended for at least 5 years to avoid long-term complications [8,10,16].

4. Conclusion

Mesenchymal hamartoma (MHL) is a rare, benign condition that could be better managed if diagnosed antenatally. Postnatally, radiological investigations (ultrasound and abdominal CT scans) are indicative of the diagnosis, with characteristic MHL findings including solid, cystic, non-vascularised or poorly vascularised liver masses. Complete resection of the tumour post-natally is an effective treatment with an excellent long-term prognosis.

Limits

It's a case report so we can't draw any relevant conclusions also, lacks precise data on the evolution of the mass during the 8 months prior to surgery.

Parental Consent for Minors

Written informed consent was obtained from the patient's parents/ legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of Competing Interest

No conflicts of interests to declare.

Ethical Approval

Ethical approval was provided by the authors' institution.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Clinical trial Number

Not applicable.

References

1. Dickinson, J. E., Knowles, S., & Phillips, J. M. (1999). Prenatal diagnosis of hepatic mesenchymal hamartoma. Prenatal Diagnosis: Published in Affiliation with the International Society for Prenatal Diagnosis, 19(1), 81-84.
2. Liu, X., Tian, S., Zhu, Z., Peng, F., Yuan, Q., Duan, X., & Yan, X. (2022). Fetal mesenchymal hamartoma of the liver: a case report and literature review. *Front Pediatr, 10*, 1016260.
3. Ammor, A., Margi, M., Lamalmi, N., Oulahyane, R., Malihy, A., Cherkaoui, A., ... & Benhmamouch, M. N. (2009). Mesenchymal hamartoma of the liver in a child: a case report. *Arch Pediatr, 16*(7), 1033-1036.
4. Kodandapani, S., Pai, M. V., Kumar, V., & Pai, K. V. (2011). Prenatal diagnosis of congenital mesenchymal

hamartoma of liver: a case report. *Case Rep Obstet Gynecol, 2011*(1), 932583.
5. Dehner, L. P., Ewing, S. L., & Summer, H. W. (1975). Infantile mesenchymal hamartoma of the liver. Histologic and ultrastructural observations. *Arch Pathol, 99*(7), 379-382.
6. Kapur, R. P., Berry, J. E., Tsuchiya, K. D., & Opheim, K. E. (2014). Activation of the chromosome 19q microRNA cluster in sporadic and androgenetic-biparental mosaicism–associated hepatic mesenchymal hamartoma. *Pediatr Dev Pathol, 17*(2), 75-84.
7. Isaacs Jr, H. (2007). Fetal and neonatal hepatic tumors. *J Pediatr Surg, 42*(11), 1797-1803.
8. Ramanujam, T. M., Ramesh, J. C., Goh, D. W., Wong, K. T., Ariffin, W. A., Kumar, G., & Taib, N. A. (1999). Malignant transformation of mesenchymal hamartoma of the liver: case report and review of the literature. *J Pediatr Surg, 34*(11), 1684-1686.
9. Khan, M. R., Binkovitz, L. A., Smyrk, T. C., Potter Jr, D. D., & Furuya, K. N. (2019). Mesenchymal hamartoma in children: a diagnostic challenge. *Case Rep Pediatr, 2019*(1), 4132842.
10. Pan, E. T., Yoeli, D., Kueht, M. L., Galvan, N. T. N., Cotton, R. T., O'Mahony, C. A., ... & Goss, J. A. (2017). Liver transplantation as definitive treatment of an unresectable mesenchymal hamartoma in a child with Beckwith–Wiedemann Syndrome. *J Surg Case Rep, 2017*(8), rjx167.
11. Chung, E. M., Cube, R., Lewis, R. B., & Conran, R. M. (2010). Pediatric liver masses: radiologic-pathologic correlation part 1. Benign tumors. *Radiographics, 30*(3), 801-826.
12. Rosado, E., Cabral, P., Campo, M., & Tavares, A. (2013). Mesenchymal hamartoma of the liver-a case report and literature review. *J Radiol Case Rep, 7*(5), 35.
13. Bejvan, S. M., Winter, T. C., Shields, L. E., Brock, B. V., Nghiem, H. V., Schmiedl, U. P., & Waldhausen, J. H. (1997). Prenatal evaluation of mesenchymal hamartoma of the liver: gray scale and power Doppler sonographic imaging. *J Ultrasound Med, 16*(3), 227-229.
14. Tsao, K., Hirose, S., Sydorak, R., Goldstein, R. B., Machin, G. A., Albanese, C. T., & Farmer, D. L. (2002). Fetal therapy for giant hepatic cysts. *J Pediatr Surg, 37*(10), 1-4.
15. Mascarello, J. T., & Krous, H. F. (1992). Second report of a translocation involving 19q13. 4 in a mesenchymal hamartoma of the liver. *Cancer genetics and cytogenetics, 58*(2), 141-142.
16. Stringer, M. D., & Alizai, N. K. (2005). Mesenchymal hamartoma of the liver: a systematic review. *J Pediatr Surg, 40*(11), 1681-1690.

Variable	β coefficient	S.D.	T-STAT	p value
PI	1.051	0.5513	1.91E+00	0.04916*
GI	0.3983	0.8148	4.89E-01	0.32
BI	-0.0852	0.06708	-1.27E+00	0.1223
PD	0.4996	0.4486	1.11E+00	0.1511
CAVEOLIN-1	0.09386	0.07664	1.23E+00	0.1301
AZUROCIDIN	-0.2622	0.2168	-1.21E+00	0.1329

Multiple R	0.9884
R square	0.9769
Adjusted R Squared	0.9539
F-TEST (value)	42.35
p value	<0.001**

Table 6: Multiple linear regression analysis of the clinical parameters and the GCF levels of caveolin-1 and azurocidin with CAL as the dependent variable in chronic periodontitis patients in the newly diagnosed diabetic group

4. Discussion

Periodontitis is a common, complex and chronic inflammatory disease in which disease progression involves intricate interactions between biofilms and the host immune system, leading to destruction of the supporting structures of the teeth. A significant interrelationship between periodontal disease and systemic health has been established and may predispose, accelerate or increase the progression of periodontitis.

Diabetes mellitus is a group of complex multisystem metabolic disorders that are a proven risk factor for periodontitis and has been supported by ample evidence. Conversely, there is evidence that periodontitis can adversely affect glycaemic control.

Caveolin-1 is an integral membrane scaffolding protein localized on the cytoplasmic side of the peripheral membrane of caveolae. It is present in several types of cells but is abundant in endothelial cells, fibroblasts, adipocytes and smooth muscle cells [16]. Recently, the colocalization of Cav-1 in hPDLCs and HGFs has been strongly demonstrated [17, 18]. In addition to its diverse cellular presence, Cav-1 is implicated in several cellular processes, such as inflammation. During inflammation, it serves as an immunomodulatory agent by modulating the activity of immune cells such as neutrophils, lymphocytes and APCs [16].

The azurophilic granules of neutrophils contain the antimicrobial protein azurocidin. Azurocidin exhibits a broad spectrum of antimicrobial activity, particularly against gram-negative bacteria. It also has chemotactic effects on monocytes/macrophages and T cells and enhances macrophage phagocytosis. During inflammation, the release of TNF-α and IL-6 from monocytes in response to lipopolysaccharide (LPS) is induced by azurocidin [19].

In light of the current understanding of the role of caveolin-1 and azurocidin in the inflammatory process, the present study was designed to estimate the GCF levels of caveolin-1 and azurocidin in selected study groups to correlate these levels with periodontal clinical parameters and to explore the possibility of using these factors as biomarkers in periodontitis and diabetes mellitus.

The mean PI value of Group III was highest, which is in accordance with the study by Campus et al [20]. This can be attributed to diabetic patients having more dental plaque and poorer oral hygiene than nondiabetic patients, which may be attributed to higher levels of glucose in gingival crevicular fluid and saliva [21].

When the mean GI was compared between groups, it was highest in Group III, similar to the findings of the study by Norma Sznajder et al., hence validating the microvascular changes in the endothelium of diabetic patients [22]. The mean BI was significantly lower in the chronic gingivitis group than in the nondiabetic and diabetic groups, similar to the findings of Tchobroutsky [23]. This may be because excess production of cytokines in diabetic patients plays an important role in both micro- and macrovascular alterations, which promote bleeding on probing [24]. Increased glucose levels in GCF may also result in altered plaque microflora, causing an increase in gingival bleeding [25].

In addition, the diabetic group showed significant increases in the mean PD and CAL, with highly significant p values (≤0.001), similar to the findings of Barnett et al. and Campbell et al. [26, 27]. Chavarry and coworkers carried out a systematic review and meta-analyses that indicated a significantly greater mean CAL and a greater mean periodontal probing depth in individuals with type 2 diabetes mellitus than in control subjects [28]. This can be explained by the fact that during the inflammatory response to the bacterial toxins in periodontal tissue, various cytokines, prostaglandins, and interleukins are released, which play a major role in the amplification of tissue destruction.

Gingival crevicular fluid comprises an assemblage of cellular and biochemical factors that determine the metabolic status of several components of the periodontium. The collection of GCF is a relatively simple and noninvasive procedure.

Therefore, the levels of Caveolin-1 and Azurocidin were estimated using GCF samples in this study.

According to the evaluation of Caveolin-1 levels, Group III had significantly greater caveolin-1 levels ($p<0.001^*$). The caveolin-1 levels were lowest in Group I. However, the caveolin-1 levels were greater in Group II than in the chronic gingivitis group, suggesting that Caveolin-1 plays a role in regulating inflammatory conditions through its effector responses for immune cells, leading to its immunomodulatory function. These findings are in accordance with those of a 2012 study by Takizawa et al., which suggested that secreted caveolin-1 derived from periodontal fibroblastic cells enhances inflammation [29]. The mechanism for this inflammatory pathway was proposed by Yamaguchi et al. in 2008, who suggested that Cav-1 is involved in IL-6, a potent inflammatory mediator, and enhances the production of cathepsin, which causes intracellular proteolysis and extracellular matrix remodelling, leading to tissue destruction in periodontitis [30]. In 2015, Lee et al. reported that Cav-1 inhibition positively regulates osteoblastic differentiation in hPDLCs, cementoblasts and osteoblasts [18].

In addition to its role in periodontal tissue, Cav-1 has been shown to be involved in systemic inflammatory conditions in several studies, as evidenced by Ohnuma et al. in 2006 and Hu et al. in 2007. These authors suggested that Cav-1 expressed in neutrophils plays an important role in the mechanism of PMN activation-mediated inflammation and that Cav-1 interaction with immune cells leads to antigen-specific T-cell activation. Additionally, overexpression of Cav-1 aggravates the inflammatory response [16,30, 31]

Several other animal studies have also shown a positive correlation between Cav-1 and chronic disease conditions [32-34].

However, in contrast to previous and present data, a study by Agarwal et al in 2010 revealed the role of Cav-1 as a negative regulator of EMMPRIN in neuroinflammation [35]. A similar result was obtained by Wang et al. in 2013, who demonstrated the colocalization of EMMPRIN in gingival tissues. Their study concluded that Cav-1 impairs EMMPRIN glycosylation, leading to decreased MMP production in periodontal disease [36].

In a study by Bae et al in 2019, Cav-1 expression increased under cytokine influence, leading to beta cell apoptosis and diabetic conditions [37]. This finding strongly explains the elevated levels of Cav-1 in group III in the present study. Various studies conducted by Ortega et al. have suggested that Cav-1 plays a role in the inflammatory response to insulin, confirming the direct contribution of Cav-1 to the maintenance of insulin in the body [38]. Under the influence of chronic inflammatory conditions and long-term glucose exposure, insulin sensitivity is compromised, leading to enhanced Cav-1 expression as an adaptive response [39,40]. In support of this, Haddad et al., in 2020, also reported that continuous exposure to high glucose concentrations increased Cav-1 and IR expression and impaired insulin signaling, leading to insulin insensitivity [41]. The possibility of newly diagnosed type 2 diabetes patients being under long-standing undiagnosed glucose exposure is likely due to elevated Cav-1 levels. In another previously conducted study by Kabayama et al. in 2007, under the influence of TNF-α-induced insulin resistance, IR and Cav-1 dynamically segregated [42]. This can indicate that under inflammatory conditions, Cav-1 tends to be dissociated from IR, leading to an increase in its level and impaired insulin signaling, as has also been suggested by the current study. Furthermore, evidence also suggests that Cav-1 may be involved in diabetes-associated inflammation because of the two-way relationship between diabetes and periodontitis.

Because of its ability to affect numerous cellular pathways, Cav-1 is also involved in various diabetes-associated complications. A 2017 study by Ding et al reported the association of Cav-1 expression with the progression of diabetic peripheral neuropathy, which is considered to be an important cause of ulcers in diabetic patients and can lead to compromised quality of life [43]. A review by Krieken and Krepinsky in 2017 showed that under high glucose conditions, Cav-1-mediated signalling leads to increased ECM accumulation, leading to DN [44]. In addition, in 2019, Bonds et al. reported a correlation between Cav-1 in type 2 diabetes mellitus and its effect on the development of Alzheimer's disease; however, this relationship is still a debated topic [45]. Nonetheless, other studies have shown the association of caveolin with diabetes complications such as diabetic retinopathy. Cardiovascular diseases such as coronary disease, cerebrovascular disease, peripheral artery disease and myocardial impairment [41].

The data of the current study and the aforementioned studies support that Cav-1 is upregulated in chronic disease conditions such as periodontitis and diabetes. Furthermore, its association with diabetes-related complications makes it a strong therapeutic molecular target for improving quality of life.

According to Pearson's correlation analysis of all three groups, caveolin-1 expression correlated significantly with clinical parameters, indicating that an increase in GI, PI, bleeding on probing, probing pocket depth and clinical attachment loss subsequently resulted in an increase in the level of Cav-1 in the GCF, indicating that Cav-1 is a biomarker that is positively associated with inflammation in periodontitis and diabetes mellitus patients.

In this study, the levels of azurocidin were also analysed, and they were significantly ($p<0.001^*$) greater in the periodontitis group than in the gingivitis group. These findings were in agreement with the findings of the first study conducted by Choi et al. in 2011. The authors revealed that azurocidin in the GCF is an upregulated protein in periodontitis patients [46]. Another study by Leppilahti et al. in 2014 revealed elevated levels of azurocidin in the GCF of patients with gingivitis and periodontitis, with higher concentrations in the periodontitis group [47]. In 2018, Guzman et al. conducted proteomic profiling of the GCF of periodontitis

patients and concluded that azurocidin was upregulated at baseline in periodontitis patients and decreased in value after periodontal therapy [48].

Recently, in 2020, Afacan and Atmaca Ilhan studied azurocidin in saliva and reported that there was a greater level of salivary azurocidin in periodontitis patients. Moreover, azurocidin has been reported to be elevated even in plasma during systemic septic conditions [49]. A review by Stock et al. in 2018 illustrated the role of neutrophil granule protein involvement in chronic inflammatory conditions such as Alzheimer's disease [50].

Our study is the first to analyse the levels of azurocidin in the GCF of patients with chronic periodontitis and newly diagnosed type 2 diabetes mellitus. The greatest amount of azurocidin was detected in Group III. These findings imply that azurocidin is elevated in chronic disease conditions such as periodontitis and diabetes. The proposed mechanism is that AZD is stored not only in azurophilic granules but also in other granules, such as secretory granules, and under chronic conditions, AZD is secreted from these granules, leading to an increase in the number and specific regulation of monocyte recruitment and activation. These factors increase cytokine release, cause destruction to the host and perpetuate inflammation. A study carried out by Huang et al. in 2018 showed strong evidence of increased neutrophil counts in newly diagnosed type 2 diabetes patients, which is in accordance with our study [20].

Pearson's correlation analysis of the periodontal parameters revealed that AZD was significantly correlated with the clinical parameters, indicating that it is a biomarker that is positively associated with inflammation in periodontitis and diabetes mellitus patients. This finding is well supported by a study conducted by Ipek et al. in 2018 in which the authors investigated the role of azurocidin and reported that azurocidin is a potent marker of inflammation [12].

Multiple linear regression analysis was used to evaluate the joint effect of all the periodontal parameters (PI, GI, BI, PD, Caveolin-1, and Azurocidin) with CAL (as the dependent variable) in all three groups, which implies that there is a significant relationship between the set of predictors and the CAL.

Although there are highly significant data related to the findings of our study, there are still some limitations. One of the major limitations of the study is that a larger number of study participants need to be recruited to overcome the variability in the results. Moreover, the levels of caveolin-1 and azurocidin need to be studied at different stages of the disease to determine the relationship between these two molecules and the disease process. Future studies can be designed to study the correlation of the expression of the molecules within groups with different variants of diabetes status and duration with HbA1c levels, which may clarify the relationship between the initiation and progression of periodontal disease.

5. Conclusion

To the best of our knowledge, the present study is the first to analyse the GCF levels of caveolin-1 and azurocidin in chronic periodontitis patients and chronic periodontitis patients with newly diagnosed type 2 diabetes. Our study revealed a correlation between the GCF levels of caveolin-1 and azurocidin in periodontitis and diabetes mellitus, suggesting that these two factors are potent markers of inflammation and have high diagnostic value. This finding underscores the importance of both molecules in normal and disease states and emphasizes the need for further research in this area.

Reference

1. Khaparde, S., Bhandari, V., Ugale, G., Jawade, R., Ardale, M., & Mundada, K. (2016). Acute phase proteins: journey of pivotal marker in periodontal disease. IOSR J Dental Med Sci, 15(7), 92-99.
2. Page, R. C., & Kornman, K. S. (1997). The pathogenesis of human periodontitis: an introduction. Periodontology 2000, 14(1), 9-11.
3. Preshaw, P. M., Alba, A. L., Herrera, D., Jepsen, S., Konstantinidis, A., Makrilakis, K., & Taylor, R. (2012). Periodontitis and diabetes: a two-way relationship. Diabetologia, 55(1), 21-31.
4. Lamster, I. B., Lalla, E., Borgnakke, W. S., & Taylor, G. W. (2008). The relationship between oral health and diabetes mellitus. J Am Dent Assoc, 139, 19S-24S.
5. Grover, H. S., & Luthra, S. (2013). Molecular mechanisms involved in the bidirectional relationship between diabetes mellitus and periodontal disease. J Indian Soc Periodontol, 17(3), 292-301.
6. Cohen, A. W., Combs, T. P., Scherer, P. E., & Lisanti, M. P. (2003). Role of caveolin and caveolae in insulin signaling and diabetes. Am J Physiol Endocrinol Metab, 285(6), E1151-E1160.
7. Jia, G., & Sowers, J. R. (2015). Caveolin-1 in cardiovascular disease: a double-edged sword. Diabetes, 64(11), 3645.
8. Elçioğlu, K. H., Kabasakal, L., Çetinel, Ş., Conturk, G., Sezen, S. F., & Ayanoğlu-Dülger, G. (2010). Changes in caveolin-1 expression and vasoreactivity in the aorta and corpus cavernosum of fructose and streptozotocin-induced diabetic rats. Eur J Pharmacol, 642(1-3), 113-120.
9. Wang, J., Yang, D., Li, C., Shang, S., & Xiang, J. (2014). Expression of extracellular matrix metalloproteinase inducer glycosylation and c aveolin-1 in healthy and inflamed human gingiva. J Periodontal Res, 49(2), 197-204.
10. Insuela, D., Coutinho, D., & Martins, M. (2020). Neutrophil Function Impairment Is a Host Susceptibility Factor to. Cells of the immune system.
11. Heinzelmann, M., Mercer-Jones, M. A., Flodgaard, H., & Miller, F. N. (1998). Heparin-binding protein (CAP37) is internalized in monocytes and increases LPS-induced monocyte activation. J Immunol, 160(11), 5530-5536.
12. Ipek, E., Yolcu, M., Yildirim, E., Altinkaynak, K., Ozbek Sebin, S., Kalkan, K., ... & Ozturk, M. (2018). A novel marker of inflammation: azurocidin in patients with ST segment elevation myocardial infarction. Int J Mol Sci, 19(12), 3797.

13. Moreno-Navarrete, J. M., & Fernández-Real, J. M. (2011). Antimicrobial-sensing proteins in obesity and type 2 diabetes: the buffering efficiency hypothesis. Diabetes Care, 34(Suppl 2), S335.
14. Alba-Loureiro, T. C., Munhoz, C. D., Martins, J. O., Cerchiaro, G. A., Scavone, C., Curi, R., & Sannomiya, P. (2007). Neutrophil function and metabolism in individuals with diabetes mellitus. Braz J Med Biol Res, 40, 1037-1044.
15. de Souza Ferreira, C., Araújo, T. H., Ângelo, M. L., Pennacchi, P. C., Okada, S. S., de Araújo Paula, F. B., ... & Rodrigues, M. R. (2012). Neutrophil dysfunction induced by hyperglycemia: modulation of myeloperoxidase activity. Cell Biochem Funct, 30(7), 604-610.
16. Hu, G., Ye, R. D., Dinauer, M. C., Malik, A. B., & Minshall, R. D. (2008). Neutrophil caveolin-1 expression contributes to mechanism of lung inflammation and injury. Am J Physiol Lung Cell Mol Physiol, 294(2), L178-L186.
17. Yamaguchi, T., Naruishi, K., Arai, H., Nishimura, F., & Takashiba, S. (2008). IL-6/sIL-6R enhances cathepsin B and L production via caveolin-1-mediated JNK-AP-1 pathway in human gingival fibroblasts. J Cell Physiol, 217(2), 423-432.
18. Lee, S. Y., Yi, J. K., Yun, H. M., Bae, C. H., Cho, E. S., Lee, K. S., & Kim, E. C. (2016). Expression of Caveolin-1 in periodontal tissue and its role in osteoblastic and cementoblastic differentiation in vitro. Calcified tissue international, 98(5), 497-510.
19. Afacan, B., & Atmaca İlhan, H. (2020). Salivary Azurocidin and Tumor Necrosis Factor-α Levels in Patients with Stage III-IV, Grade C Periodontitis. Ege Üniversitesi Diş Hekimliği Fakültesi Dergisi, 41(1), 47-54.
20. Campus, G., Salem, A., Uzzau, S., Baldoni, E., & Tonolo, G. (2005). Diabetes and periodontal disease: A case-control study. J Periodontol, 76(3), 418-425.
21. Mohamed, H. G., Idris, S. B., Ahmed, M. F., Bøe, O. E., Mustafa, K., Ibrahim, S. O., & Åstrøm, A. N. (2013). Association between oral health status and type 2 diabetes mellitus among Sudanese adults: a matched case-control study. PloS one, 8(12), e82158.
22. Sznajder, N., Carraro, J. J., Rugna, S., & Sereday, M. (1978). Periodontal findings in diabetic and nondiabetic patients J Periodontol, 49(9), 445-448.
23. Tchobroutsky, G. (1978). Relation of diabetic control to development of microvascular complications. Diabetologia, 15(3), 143-152.
24. Witztum, J. L. (1997). Role of modified lipoproteins in diabetic macroangiopathy. Diabetes, 46(Supplement_2), S112-S114.
25. Ambon, J. J., Reynolds, H., Fisher, J. G., Shlossman, M., Dunford, R., & Genco, R. J. (1988). Microbiological and immunological studies of adult periodontitis in patients with noninsulin-dependent diabetes mellitus. J Periodontol, 59(1), 23-31.
26. Barnett, M. L., Baker, R. L., Yancey, J. M., MacMillan, D. R., & Kotoyan, M. (1984). Absence of periodontitis in a population of insulin-dependent diabetes mellitus (IDDM) patients. J Periodontol, 55(7), 402-405.
27. Campbell, M. J. A. (1972). Epidemiology of periodontal disease in the diabetic and the non-diabetic. Aust Dent J, 17(4), 274-278.
28. Chávarry, N. G., Vettore, M. V., Sansone, C., & Sheiham, A. (2009). The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. Oral Health Prev Dent, 7(2), 107-27.
29. Takizawa, N., Sawada, S., Chosa, N., Ishisaki, A., & Naruishi, K. (2013). Secreted caveolin-1 enhances periodontal inflammation by targeting gingival fibroblasts. Biomed Res, 34(1), 1-11.
30. Ohnuma, K., Inoue, H., Uchiyama, M., Yamochi, T., Hosono, O., Dang, N. H., & Morimoto, C. (2006). T-cell activation via CD26 and caveolin-1 in rheumatoid synovium. Mod Rheumatol, 16(1), 3-13.
31. Lv, X. J., Li, Y. Y., Zhang, Y. J., Mao, M., & Qian, G. S. (2010). Over-expression of caveolin-1 aggravate LPS-induced inflammatory response in AT-1 cells via up-regulation of cPLA2/p38 MAPK. Inflamm Res, 59(7), 531-541.
32. Gurley, J. M., Gmyrek, G. B., McClellan, M. E., Hargis, E. A., Hauck, S. M., Dozmorov, M. G., ... & Elliott, M. H. (2020). Neuroretinal-derived caveolin-1 promotes endotoxin-induced inflammation in the murine retina. Invest Ophthalmol Vis Sci, 61(12), 19-19.
33. Li, X., Gu, X., Boyce, T. M., Zheng, M., Reagan, A. M., Qi, H., ... & Elliott, M. H. (2014). Caveolin-1 increases proinflammatory chemoattractants and blood–retinal barrier breakdown but decreases leukocyte recruitment in inflammation. Invest Ophthalmol Vis Sci, 55(10), 6224-6234.
34. Medina, F. A., De Almeida, C. J., Dew, E., Li, J., Bonuccelli, G., Williams, T. M., ... & Lisanti, M. P. (2006). Caveolin-1-deficient mice show defects in innate immunity and inflammatory immune response during Salmonella enterica serovar Typhimurium infection. Infect Immun, 74(12), 6665-6674.
35. Agrawal, S. M., & Yong, V. W. (2011). The many faces of EMMPRIN—roles in neuroinflammation. Biochim Biophys Acta, 1812(2), 213-219.
36. Wang, X. M., Kim, H. P., Song, R., & Choi, A. M. (2006). Caveolin-1 confers antiinflammatory effects in murine macrophages via the MKK3/p38 MAPK pathway. Am J Respir Cell Mol Biol, 34(4), 434-442.
37. Bae, Gong Deuk, Eun-Young Park, Kyong Kim, Se-Eun Jang, Hee-Sook Jun, and Yoon Sin Oh. "Upregulation of caveolin-1 and its colocalization with cytokine receptors contributes to beta cell apoptosis." Sci Rep 9, no. 1 (2019): 16785.
38. Palacios-Ortega, S., Varela-Guruceaga, M., Algarabel, M., Milagro, F. I., Martínez, J. A., & De Miguel, C. (2015). Effect of TNF-alpha on caveolin-1 expression and insulin signaling during adipocyte differentiation and in mature adipocytes. Cell Physiol Biochem, 36(4), 1499-1516.
39. Palacios-Ortega, S., Varela-Guruceaga, M., Milagro, F. I., Martínez, J. A., & De Miguel, C. (2014). Expression of Caveolin 1 is enhanced by DNA demethylation during adipocyte differentiation. status of insulin signaling. PloS one, 9(4), e95100.
40. Palacios-Ortega, S., Varela-Guruceaga, M., Martínez, J. A., de Miguel, C., & Milagro, F. I. (2016). Effects of high glucose on caveolin-1 and insulin signaling in 3T3-L1 adipocytes. Adipocyte, 5(1), 65-80.
41. Haddad, D., Al Madhoun, A., Nizam, R., & Al-Mulla,

F. (2020). Role of caveolin-1 in diabetes and its complications. Oxid Med Cell Longev, 2020(1), 9761539.
42. Kabayama, K., Sato, T., Saito, K., Loberto, N., Prinetti, A., Sonnino, S., ... & Inokuchi, J. I. (2007). Dissociation of the insulin receptor and caveolin-1 complex by ganglioside GM3 in the state of insulin resistance. Proc Natl Acad Sci U S A, 104(34), 13678-13683.
43. Ding, M., Zhu, X., Ye, L., Wang, M., Cui, Y., Xu, J., ... & Wang, P. (2017). Association between Caveolin-1 expression and pathophysiological progression of femoral nerves in diabetic foot amputation patients. Open Life Sciences, 12(1), 308-314.
44. Van Krieken, R., & Krepinsky, J. C. (2017). Caveolin-1 in the pathogenesis of diabetic nephropathy: potential therapeutic target?. Curr Diab Rep, 17(3), 19.
45. Bonds, J. A., Shetti, A., Bheri, A., Chen, Z., Disouky, A., Tai, L., ... & Lazarov, O. (2019). Depletion of caveolin-1 in type 2 diabetes model induces Alzheimer's disease pathology precursors. J Neurosci, 39(43), 8576-8583.
46. Choi, Y. J., Heo, S. H., Lee, J. M., & Cho, J. Y. (2011). Identification of azurocidin as a potential periodontitis biomarker by a proteomic analysis of gingival crevicular fluid. Proteome Sci, 9(1), 42.
47. Leppilahti, J. M., Hernández-Ríos, P. A., Gamonal, J. A., Tervahartiala, T., Brignardello-Petersen, R., Mantyla, P., ... & Hernández, M. (2014). Matrix metalloproteinases and myeloperoxidase in gingival crevicular fluid provide site-specific diagnostic value for chronic periodontitis. J Clin Periodontol, 41(4), 348-356.
48. Guzman, Y. A., Sakellari, D., Papadimitriou, K., & Floudas, C. A. (2018). High-throughput proteomic analysis of candidate biomarker changes in gingival crevicular fluid after treatment of chronic periodontitis. J Periodontal Res, 53(5), 853-860.
49. Yang, Y., Liu, G., He, Q., Shen, J., Xu, L., Zhu, P., & Zhao, M. (2019). A promising candidate: heparin-binding protein steps onto the stage of sepsis prediction. J Immunol Res, 2019(1), 7515346.
50. Dowey, R., Iqbal, A., Heller, S. R., Sabroe, I., & Prince, L. R. (2021). A bittersweet response to infection in diabetes; targeting neutrophils to modify inflammation and improve host immunity. Front Immunol, 12, 678771.