

Role of Growth Differentiation Factor15 in pediatric cardiac patients

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Abstract

Background: The most common kind of birth abnormality is a heart problem. When the heart doesn't form properly during pregnancy or birth, it's called a congenital heart defect. CHDs are associated with high rates of mortality and disability. Multiple processes are controlled by the cytokine growth differentiation factor-15 (GDF-15). Because of its continuous overexpression in both CVD and diabetes, GDF-15 is recommended as a biomarker for the existence and severity of both illnesses. In contrast, a large body of research indicates that GDF-15 has a protective role in the regulation of inflammation, endothelial cell function, insulin sensitivity, and weight gain, and is cardioprotective in myocardial infarction (MI).

Objectives: Aim of the work is to give highlight on (GDF15) in pediatric cardiac diseases of varies aetiologies.

Conclusion: It has been discovered that the cytokine growth differentiation factor-15 (GDF-15) is elevated in a number of clinical states, including hypertension, cardiovascular illness, and oxygen deprivation. GDF-15 is also found to be elevated in HF and PH (pulmonary hypertension). An increased level of GDF-15 is seen in newborns and children with PH-CHD, suggesting its use as a diagnostic biomarker.

Keywords: Growth Differentiation Factor15; Congenital heart diseases; Pediatric cardiac disease.

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Introduction

The most common kind of congenital abnormality involves the heart. When the heart doesn't form properly during pregnancy or birth, it's called a congenital heart defect. Consistent heart problems are associated with a high risk of death and serious illness. For this reason, cardiac injury is irreparable. (suluba et al., 2020).

There are many types of congenital heart diseases. Most affect the walls, valves, or blood vessels; some are serious and may need several surgeries and treatment (Berezin et al., 2018).

The prevalence of congenital heart disease (CHD) varies from 3.5-17.5 per 1000 live births, making it one of the most frequent congenital impairments. More and more children are dying from them, particularly in third world nations.

Relationship between cardiac development and congenital cardiac diseases:

Prenatal diagnosis of congenital heart disease (CHD) is challenging because the developing infant depends on both the right and left sides of the heart for oxygenation and feeding, and because shunts exist between the atrium and the arterial system. Since one side of the heart may compensate for an anomaly on the other side, the vast majority of babies with CHD do not exhibit obvious indications of cardiac failure throughout fetal life. (Hunter and Simpson, 2014).

Aetiology and pathophysiology of congenital heart disease:

In industrialized nations, the two leading causes of pediatric heart failure are congenital heart defects and cardiomyopathies. (Kantor and Mertens, 2010).

To put it another way, congenital heart failure is common in infants who have volume overload situations such large post-tricuspid left-to-right (L-R) shunts or specialized atrioventricular and semilunar valve severe regurgitations (CHF). (Das, 2018).

In addition, HF may develop from myocardial dysfunction due to a broad range of anatomical abnormalities.

Classification of congenital heart diseases:

Atrial septal defect(ASD): The right atrium is formed when the fetal sinus venosus is reabsorbed into the developing structure and the septum primum and septum secundum fuse to generate endocardial cushions (RA).

Ventricular septal defect(VSD): The merging of separate septal components during embryogenesis leads to this abnormality in the ventricular septum.

Patent ductus arteriosus: Fetal blood flow from the RV may return to the placenta through the descending aorta and avoid the fetus' nonfunctional lungs thanks to the ductus. Arteriolar smooth muscle contraction, a process induced by rise in postnatal systemic oxygen level, closes the ductus in most neonates after 72 hours after birth. (Hermes-DeSantis and Clyman, 2006).

Tetralogy of Fallot: It is a complex heart defect having following four components: (a) PS, i.e., the valve between the RV and lungs become narrow; (b) hypertrophy of RV, i.e., lower chamber of the heart become enlarged; (c) VSD; and (d) overriding aorta, i.e., enlarged aorta located over a VSD.

Transposition of great arteries (TGA):

It is the most prevalent congenital cardiac cyanotic lesion.

Pulmonary hypertension:

Congenital cardiac defects often lead to pulmonary hypertension (PH), a potentially fatal condition.

Heart failure:

There is an increasing need for novel and discriminative biomarkers to aid in the management of HF, which has a complicated pathogenesis characterized by pluriorganic involvement, progressive deteriorating nature, and a lack of response to standard treatments. (Chow et al., 2017).

Cardiomyopathy:

Dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathy are the three most frequent physiologic subtypes of cardiomyopathy. Diseases of the heart muscle (cardiomyopathies) may occur even in the absence of an obvious structural or functional abnormality. For youngsters, dilated and hypertrophic cardiomyopathies outnumber restrictive cardiomyopathy by a wide margin. (Alizadehasl et al., 2021).

Rheumatic heart disease:

The condition known as rheumatic heart disease (RHD) is caused by group A streptococcal infection. Complex streptococcal infection comes from several elements, including the host's genetics, the pathogen, and the environment.

Growth Differentiation Factor-15:

Names for growth differentiation factor-15 include macrophage inhibitory cytokine-1 (MIC-1), placental transforming growth factor-beta (pTGFB), prostate-derived factor (PDF), and placental bone morphogenetic protein (BMP-15) (PLAB). The TGF- β family of growth factors includes the growth differentiation factor-15 (GDF-15), however it is distinct from the other members of the family.

The TGF- β superfamily is identified by a cysteine knot, which is composed of seven conserved cysteine residues. Sequence conservation for GDF-15 orthologs is the lowest of any superfamily member.

FISH studies have pinpointed the human GDF15 locus to chromosome 19p12.1-13.1, where it has been shown to consist of a single intron 1820 bp in length.

Researchers have shown that genetics have a significant impact in setting GDF15 levels. Allelic variations on the vicinity of the GDF15 gene on chromosome 19p13.11 have been observed to be significantly correlated with GDF15 levels. (J.E. Ho, et al.2012).

Pro-GDF15 monomer (~40 kDa), pro-GDF15 dimer (~80 kDa), and mature dimer (~30 kDa) are all forms of GDF15 that are

produced during protein synthesis. The N-terminal signal peptide in the GDF15 precursor protein is crucial for its intracellular trafficking and secretion.

Mature TGF- β 1, BMP-2, and GDF-15 proteins from rats, mice, and humans have 99–100% sequence identity. Additionally, despite low to nonexistent constitutive expression and the possibility of activation in numerous cell types under stress circumstances, the promoter regions for GDF-15 are located exclusively outside of reproductive organs. Full-length GDF-15 is 308 amino acids long, including the 29-amino-acid signal peptide, 167-amino-acid pro-domain, and 112-amino-acid mature form.

GDF-15 is produced in the cell and secreted as a pro-protein with an extracellular matrix pro-domain (ECM). This leads to the accumulation of dormant stromal reserves that, upon proteolytic cleavage, may rapidly release abundant amounts of GDF-15. (Bauskin et al.,2010).

The major immunohistochemical target of GDF-15 is its pro-domain, which is retained in the ECM and stains like a surface protein. The furine-like cleavage site RXXR in GDF-15 is thought to be a target for the subtilisin/kexin type I proprotein convertases furin (PCSK3), PCSK5, and PCSK6. (Li et al., 2018).

Matrix metalloproteinase (MMP)-26 may have a role in the processing and maturation of placental cytotrophoblasts. (Li et al., 2014). However, cleavage by membrane-type-1-matrix metalloproteinase inhibited autocrine activities in cancer cells (MT1-MMP) (Abd El-Aziz et al., 2007).

Contrary to expectations, GDF-15 is also localized in the nucleus, where it has been shown to interfere with the Smad complex and hence block the Smad pathway. (Min et al., 2016).

As a disulfide-linked homodimer, GDF-15 is secreted into the body after processing is complete. Renal clearance occurs quite quickly (approximately 3 hours) for mature GDF-15 because of its small size (25 kDa per dimer) (Wischhusen et al., 2020).

GDF-15 expression is controlled by androgens and the vitamin D metabolite calcitriol in normal humans. This occurs in both the placenta and the prostate. (Nazarova et al., 2006).

Several common organs are quite silent, including the kidney, colon, stomach, bladder, gall bladder, pancreas, liver and endometrium. (Uhlen et al., 2015).

Both healthy and sick cardiomyocytes, adipocytes, macrophages, endothelium, and vascular smooth muscle cells (VSMCs) express GDF-15. (Tsai et al., 2018).

A tissue-specific activation mechanism for GDF-15 involves inflammatory and stress-related proteins. These proteins include IL-1 β , TNF- α , IL-2, and MCSF-1. (Adela & Banerjee, 2015).

During operations, GDF-15 may be induced by a number of factors, including drugs, cellular stress, and temporary loss of blood flow (Guenancia et al., 2015) It would explain why GDF-15 mRNA expression is often so high in tissue samples taken during surgery. Even yet, physiological GDF-15 levels are either missing or extremely low in healthy humans in most organs where GDF-15 expression may be increased. (Uhlen et al., 2015).

Reports of increased GDF-15 levels in cancer patients are common, and this cytokine was shown to be the most strongly overexpressed in tumors. Research using the Protein Atlas revealed that GDF-15 expression was much greater in certain cancer types than others. This was notably true for malignancies of the prostate, urothelium, kidney, melanoma, colon, cervix, breast, endometrium, thyroid, and pancreas. (Uhlen et al., 2017).

The Cancer Genome Atlas (TCGA) database found GDF-15 mRNA overexpression in many types of cancer, including prostate cancer (which has the highest levels), breast cancer, liver cancer, colorectal cancer, cervical cancer, renal cell carcinoma, hepatocellular carcinoma, and cholangiocellular carcinoma. (Cerami et al., 2012).

A member of the GDNF family, glial cell-derived factor-15 (GDF-15) interacts with -like receptors (GFRAL). Neuronal GFRAL is a high-affinity GDF-15 receptor that has a tenuous evolutionary link with the TGF-receptor family. (Mullican et al., 2017).

GFRAL causes GDF-15-mediated anorexia and is expressed only in the human brain stem. (Mullican & Rangwala, 2018).

Despite significantly increased GDF-15 blood levels, pregnancy is not often accompanied by the cachexia and anorexia that should result from GDF-15-dependent activation of GFRAL. Further research is needed to discover if GFRAL is required for the consequences of increased GDF-15 expression in metabolic disorders, tissue damage, inflammation, and cancer. GFRAL-independent activities of GDF-15 seem feasible, given that its physiological effects include a variety of actions on cell types with no detectable GFRAL expression. This opens the door for GDF-15 to interact with receptor systems we haven't even discovered yet. (Wischhusen et al., 2020).

Mechanisms of Action:

Because GDF-15 is involved in such a wide variety of tissues and cellular processes, it is crucial to learn more about how it works, which receptors it interacts with, and what signals it sends in response. The importance of GDF-15 as a weight regulator is now well-established. (Johnen et al., 2007).

In an effort to identify a receptor with which it may bind and, from that, determine the signaling pathways that may be triggered as a result. Based on these observations, it was postulated that GDF-15 might transmit signals through SMAD2/3 contact with the TGFRII receptor. Four studies looked at how GDF-15 bound to different TGF-receptors and ultimately settled on GFRAL as the receptor mediating GDF-15's metabolic effects. There is currently just one identified GDF-15 receptor, and it happens to be a GDNF receptor family member called GFRAL. GFRAL, like other GDNF receptors, activates ERK and AKT/protein kinase B pathways but not conventional TGF- signaling pathways via

its interaction with its co-receptor RET (most effectively with RET51). (Wischhusen et al., 2020).

Role of Growth Differentiation Factor15 on Metabolic Conditions:

Anorexia and cachexia are metabolic illnesses characterized by a lack of appetite, slow but steady weight loss, reduced adipose tissue, and atrophy of skeletal muscle and organs. We don't fully understand the released substances from tissues or cancer cells that cause this illness. Anorexia and cachexia affect about 80% of people with late-stage cancer. Twenty to thirty percent of all cancer fatalities are attributable to metabolic abnormalities, making them a major area of unmet medical need. (Lerner et al., 2015).

Increased GDF-15 serum levels have been linked to anorexia and cachexia, two forms of malnutrition. The hypothalamus is the brain region responsible for regulating feeding behavior. (Neary et al., 2004).

Both anorexia and cachexia are induced by GDF-15, and its effects have been traced to neurons in the area postrema and the nucleus of the solitary tract. (Tsai et al., 2016).

GDF-15 was also shown to be linked to anorexia/cachexia in patients with a variety of other diseases, such as hepatocellular carcinoma. (Borner et al., 2017).

Antibodies directed against GDF-15 could be able to reverse weight loss. Since GDF-15 is the primary regulator of both anorexia and cachexia, therapeutically modulating GDF-15 may be useful. (Lerner et al., 2016).

Metformin boosts GDF-15 production as well (GDF-15). The anti-obesity benefits of this widely used medication for type 2 diabetes may be attributed to GDF-15. (Coll et al., 2019).

Because of this, GDF-15 and GFRAL might one day be used as pharmacological targets for controlling appetite and energy intake.

Research from the Novartis Institute for Biomedical Research demonstrates that GDF-15 is increased in response to supraphysiologic

injections of GDF-11, suggesting that elevated GDF-11 levels may contribute to the cancer-related anorexia and muscle loss. However, inhibiting GDF-15 was more effective against anorexia than blocking GDF-11, which may prevent anorexia but not muscle loss. (Jones et al., 2018).

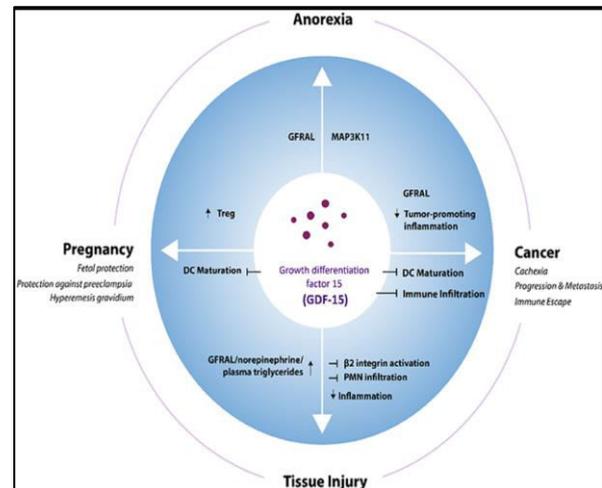


Fig. 1. GDF-15 in many diseased and healthy conditions. In diverse physiological and pathological contexts, GDF-15 acts on GFRAL and maybe additional, as-yet-unidentified receptors to either activate or inhibit certain cellular processes. Dendritic cells (DCs) and T regulatory cells (Tregs). (Wischhusen et al., 2020).

Role of Growth Differentiation Factor15 in pediatric cardiac patients:

Following acute damage to the heart, liver, kidney, or lung, GDF-15 levels rise. (Zimmers et al., 2006).

Recent research has linked elevated plasma GDF 15 levels to an increased the risk of death in individuals with acute coronary syndrome and acute heart failure. (Jankovic-Tomasevic et al., 2016).

In patients with chronic heart failure, increases in GDF-15 over time have been linked to increasing heart failure and poor outcomes. (Gaggin et al., 2014).

Research into the function and prognostic importance of cardiovascular blood biomarkers at the molecular level of the cardiac re-modelling process may complement established diagnostic techniques for cardiovascular disorders. (Önal et al., 2021).

Growth Differentiation Factor15 in the prediction of cardiovascular risk:

Patients experiencing chest pain, shortness of breath, heart failure, or a recent myocardial infarction should not rely on GDF-15 as a diagnostic tool. Possible reasons for this include its wide distribution and lack of specificity, which together make it a good predictor of cardiovascular events; abnormalities are determined by processes that ultimately reflect oxidative stress, apoptosis, chronic inflammation, and repair; and these processes are influenced by lifestyle, comorbidities, and aging. The majority of studies indicated that these associations remained even after researchers accounted for potential confounding factors such as age, sex, BMI, diabetes, hypertension, smoking, LVEF, natriuretic peptides, cardiac troponins, renal function, and medication use. (Di Candia et al., 2021).

The relations between GDF-15, cardiovascular disease and cancer :

In order for normal tissues to transition into a neoplastic state, there must be an imbalance between the activation of oncogenes and the protective suppression of tumor suppressor genes. This "immune surveillance" action draws immune cells (mostly macrophages) to the tumor location, where they then enter the tumor and coordinate the clearance processes. (Ratnam et al., 2017).

GDF-15 plays a critical role in the complex interplay among both tumor cells and macrophages. GDF-15 inhibits tumor development in vitro by inhibiting NF-KB-mediated pro-apoptotic activity in macrophages and lowering TNF-alpha and nitric oxide production (NO). Many malignancies, including those of the breast, colon, pancreatic, and prostate, have elevated GDF-15 expression. (Narayan et al., 2020).

Chronic inflammation, endothelial dysfunction, and oxidative stress are all mechanisms through which GDF-15 has been associated to the development and progression of a broad range of illnesses, including cardiovascular disease, cancer, and others. (Narayan et al., 2020).

The growth differentiation factor 15 has a major impact on the subcellular communication between aging, obesity, CHIP (clonal hematopoiesis of indeterminate potential), neoplasia, and cardiovascular risk (GDF-15) (Libby et al., 2019).

It is for these reasons that GDF-15 is held in high esteem as a marker of biological significance. on the other hand, GDF-15 concentrations that are abnormally high may serve as an early signal of pathological processes that carry a higher risk and need more study. (Wang et al., 2012).

GDF15 in congenital heart diseases:

The majority of heart problems in children are caused by congenital heart defects (CHD). They caused by abnormal cardiac vascular development in fetal period. The signs of heart failure in infants are not clear, and specific diagnostic methods are insufficient.

There is still a lack of simple laboratory test indicators for early diagnosis of CHD combined with chronic heart failure in infants, and there are still difficulties in early diagnosis. Therefore, finding detection factors is of great significance for diagnosis of diseases.

The clinical manifestations of CHD are similar to heart failure, so the diagnosis becomes more difficult when the two appear together. GDF-15 studied in CHD in infants combined with chronic heart failure high level of GDF-15 can be detected in patients with CHD and chronic heart failure, and their levels are positively correlated with different cardiac function levels

GDF-15 and heart failure:

There is an increasing need for novel and discriminative biomarkers to aid in the management of HF, which has a complicated pathogenesis characterized by pluriorganic involvement, progressive deteriorating nature, and a lack of response to standard treatments. (Chow et al., 2017).

Higher GDF-15 levels are seen in the majority of individuals with HF; these levels are correlated with disease severity and functional impairment and are independently linked to the likelihood of hospitalization and death. GDF-15 is similarly high in all three groups, despite BNP, NT-proBNP, and hs-TnT concentrations being lower in patients with HFpEF compared to those with HFrEF or HFpEF with intact ejection fraction. Since HFpEF is a growing phenotype that is largely connected to a chronic inflammatory state, such as hypertension, metabolic syndrome, aging and obesity, the ability of GDF-15 to show this continuous low-grade inflammatory condition appears to be crucial. (chan et al,2016)

GDF15 in pulmonary hypertension:

Biomarkers for pulmonary hypertension from congenital heart disease (PH-CHD) include B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptides (NT proBNP) (GDF-15). GDF-15 levels were significantly higher in PH-CHD patients than in CHD patients. Researchers found that hypoxic and pressure-overload situations, both of which are aggravated by PH, result in increased levels of plasma growth differentiation factor-15 (GDF-15). (Xu J, Kimball TR, Lorenz JN, Brown DA, Bauskin AR. et al. 2006).

PPH and skeletal muscle atrophy: an atypical case of GDF-15/TAK-1 signaling. GDF-15 is overexpressed in pulmonary vascular endothelial cells in rat monocrotaline (MCT) and mouse SU5416/hypoxia models of pulmonary hypertension (PH).

An increase in circulating GDF-15 levels is related with the development of PAH, and this rise corresponds with a reduction in tibialis anterior (TA) muscle fiber diameter in both

animal models and very weakly with quadriceps volume and function in people with PAH. In vitro tests with cultured skeletal muscle cells have also demonstrated this link. These data support the concept that GDF-15 mediates the impact of pulmonary circulation on PAH muscle hypertrophy.

PAH is a systemic illness with metabolic, inflammatory, genetic, and epigenetic abnormalities that go beyond pulmonary circulation, thus this conclusion is not a total surprise.

GDF15 in cardiomyopathy:

GDF-15 is highly expressed by myocardial cells especially in those exposed to hypoxia, wall stress or ischemia.

Many peptide growth factors/cytokines, such as angiotensin II (Ang II), insulin-like growth factor 1 (IGF-1), endothelin-1 (Endo 1), apolipoprotein B (ANP), b-type natriuretic peptide (BNP), cardiotrophin-1, tumor necrosis factor-alpha, interleukin-6 (IL-6), interleukin-1 (IL-1), epidermal growth factor (EG Among the TGF- family of proteins, growth-differentiation factor 15 has only lately been fully described (GDF15)s(Force T, Michael A, Kilter H, Haq Set,al.2002).

Natriuretic peptide signaling may be analogous to the activation of GDF15 expression by heart disease-causing events. Both ANF and BNP indicate a protective and antihypertrophic response in their receptors and are released in response to acute and chronic stimulation associated with heart injury and long-term disease, respectively. (Woods RL.et,al2004).

It's possible that GDF15 has a similar function, and that targeting it therapeutically might be an innovative way to treating hypertrophic and dilated cardiomyopathy. Heart disease risk factors and the occurrence of cardiovascular events were shown to be linked with GDF15 blood levels. (Brown DA, Breit SN, Buring J, Fairlie WD, Bauskin AR, Liu T, Ridker PM.et,al.2002).

GDF15 in rheumatic heart disease

Atrial fibrillation is the most common clinical manifestation of a wide range of heart diseases and heart-related ailments (AF). (Shiran A, Sagie A. et al 2009).

AF can seriously affect human health, in addition, which could cause serious cardiovascular and cerebrovascular events, has a high morbidity and mortality. It is reported that the expression level of GDF-15 is significantly increased in myocardial tissue and peripheral blood (Fuernau G, Poenisch C, Eitel I, de Waha S, Desch S, Schuler G, Adams V, Werdan K, Zeymer U, Thiele H. et al 2014)

Similarly, GDF-15 was shown to be higher in the peripheral blood of individuals with chronic heart failure, and this elevation was linked to a worse prognosis for heart failure. (Wollert KC, Kempf T. et al 2012).

Although GDF-15 has been linked to cardiac fibrosis as a potential biological biomarker of AF's severity, it remains uncertain whether or not this link really exists. So, we set out to see whether there was any connection between GDF-15 and atrial fibrosis in those who suffered from both atrial fibrillation and rheumatic heart disease.

Conclusion:

High level of GDF15 can be detected in pediatric cardiac patients is positively correlated with different cardiac function levels .with aggravation of disease degree,the measured level increased,indicating that this biomarker has important significance in the treatment of disease and prognosis.

Abbreviations:

GDF15: Growth differentiation factor-15.

CHDs: congenital heart diseases

CVD: cardio vascular disease.

MI: myocardial infarction.

HF: heart failure

PH: pulmonary hypertension.

RA: right atrium.

RHD: rheumatic heart diseas.

PS: pulmonary stenosis.

RV: right ventricle.

ASD: atrial septal defect.

VSD: ventricular septal defect.

TGA: transposition of great arteries.

MIC-1: macrophage inhibitory cytokine.

NAG: non-steroidal anti-inflammatory drug-inducible gene.

PTGFβ: placental transforming growth factor-beta.

PDF: prostate derived factor.

PLAB: placental bone morphogenetic protein.

TGF-β: Transforming growth factor B.

ECM: Extracellular matrix.

MMP: matrix metalloproteinase

MT1-MMP: membrane-type 1-matrix metalloproteinase.

IL: interleukin.

TNF: tumor necrosis factor.

MCSF: macrophage colony-stimulating factor (MCSF).

GDNF: glial cell-derived neurotrophic factor.

CHIP: clonal hematopoiesis of indeterminate potential.

FISH: fluorescence *in situ* hybridization.

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