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Role of Umbilical cord C-peptide in assessment of hypoglycemia in neonates of diabetic mothers

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Abstract:Background: C-peptide (connecting peptide) connects alpha and beta chains of proinsulin, which are formed in the endoplasmic reticulum following the removal of the signal peptide of pre-proinsulin. It is secreted from the beta cells of islets of Langerhans of the endocrine pancreas when proinsulin is cleaved into insulin and C-peptide. It plays an important role in the correct folding of insulin and the formation of disulfide bridges.An area of growing research is the question as to whether c-peptide can be used to predict diabetes complications. Lower c-peptide values have been associated with poorer glycemic control and hence increased HbA1c values. Despite marked declines in neonatal mortality nowadays, diabetes mellitus (DM) with pregnancy either gestational (GDM), type 1, or 2 is still associated with a risk of maternal, fetal, and neonatal morbidities and mortalities. Moreover, its prevalence did not decline, as GDM was about 8.74%. Infants of a diabetic mother (IDM) often have complications closely linked to fetal hyperglycemia and hyperinsulinemia, induced by maternal hyperglycemia.

Keywords: Umbilical Cord, C-Peptide, IDM

Introduction

Globally, 366 million people are suffering from diabetes mellitus (DM), and by 2030, this number is likely to double. Along with an increase in the prevalence of DM, there seems to be an increasing prevalence of Gestational DM (GDM), i.e., DM diagnosed during pregnancy. International Diabetic Federation (IDF) estimated that 20.9 million or 16.2% of babies born to women in 2015 were exposed to some form of hyperglycemia during pregnancy. Of this 85.1 % were estimated to be due to GDM, 7.4% were due to other

types of DM first detected during pregnancy and 7.5% were due to DM detected prior to pregnancy, termed as pre-gestational Diabetes Mellitus (Pre GDM) **(1)**.

DM complicating pregnancy not only influences maternal (preeclampsia, polyhydramnios, stillbirth, need for caesarean section), fetal (congenital anomalies, macrosomia) and neonatal (hypoglycemia, birth injuries, polycythemia, hyperbilirubinemia) outcomes, but also increases the subsequent risk of developing Type 2 DM (T2DM) in mother as well as the baby. Studies indicate that the severity of these complications is proportional to the level of maternal hyperglycemia. Hence, meticulous glycemic control during the periconceptional and antenatal period prevents or at least decreases the risk of most complications **(2)**.

Gestational and pre-gestational diabetes mellitus

GDM is defined as diabetes which occurs during pregnancy that is not clearly overt diabetes. The underlying pathogenesis is similar to that observed in T2DM, i.e., decrease in insulin sensitivity with advancing gestation. The prevalence of GDM is nearly 7.5% and it is increasing secondary to increasing rates of maternal overweight and obesity. Usually, GDM is transient in pregnancy and improves shortly after delivery. However, GDM can be the precursor to T2DM for many women and needs follow up **(3)**.

C-peptide (connecting peptide) connects alpha and beta chains of proinsulin, which are formed in the endoplasmic reticulum following the removal of the signal peptide of pre-proinsulin. It is secreted from the beta cells of islets of Langerhans of the endocrine pancreas when proinsulin is cleaved into insulin and C-peptide. It plays an important role in the correct folding of insulin and the formation of disulfide bridges. C-peptide is removed in the Golgi apparatus from proinsulin resulting in the formation of the mature insulin molecule with both alpha and beta chains bound together by disulfide bonds **(4)**.

Both insulin and C-peptide are stored in secretory vesicles and released in equimolar concentrations upon stimulation of beta cells by glucose and other secretagogues. The most important indications for measurement of C-peptide levels include the differential diagnosis of fasting hypoglycemia with hyperinsulinism and as a measure of insulin secretory reserve. Once secreted, both insulin and C-peptide are routed through the liver. In the liver, insulin binds to its receptors and initiates glucose uptake, inhibits gluconeogenesis, glycogenolysis, and ketogenesis and is degraded within 5 to 10 minutes. C-peptide, on the other hand, has limited degradation in the liver and is degraded by the kidneys. Hence, the half-life of C-peptide is around 30 to 35 minutes **(5)**.

C-peptide is a 31-amino acid polypeptide and is negatively charged. In mammals, the 8 residues (positions 1, 3, 6, 11, 12, 21, 27, and 31) are conserved, and the C-terminal pentapeptide has been shown to interact with the cell membrane and elicit signaling pathways. Although the exact mechanism of binding is not known, the binding characteristics and the intracellular effects could be modified by pertussis toxin, suggesting that the G-protein coupled receptors might be involved **(6)**.

The binding of C-peptide was shown to elevate the intracellular calcium levels. It also can induce phospholipase C, protein kinase C isoforms, Rho A, and p38 MAPK in renal tubular cells and fibroblasts. Activation of the PI3 kinase, Akt, and PPAR-gamma is also observed in fibroblasts, myoblasts, renal tubular cells, and lymphocytes. In endothelial cells, C-peptide was shown to induce nitric oxide release by enhancing the expression of eNOS mRNA and protein in aortic endothelial cells. It was also shown to stimulate Na, K-ATPase in renal tubular cells in vitro **(7)**.

C-peptide was also shown to possess several anti-inflammatory, cytoprotective, and anti-apoptotic effects in various cell types. Under physiological conditions, C-peptide was shown to inhibit the formation of reactive oxygen species (ROS) via RAC1-mediated inhibition of NAD(P)H oxidase in endothelial cells of streptozotocin (STZ)-diabetic mice **(7)**.

C-peptide could inhibit ROS-mediated activation of transglutaminase 2, thereby inhibiting apoptosis. It also exerted the anti-apoptotic effect by inhibiting caspase 3 activation and enhancing the anti-apoptotic protein,

C-Peptide in clinical practice

C-peptide is a useful and widely used method of assessing pancreatic beta cell function. After cleavage of proinsulin, insulin and the 31-amino-acid peptide c-peptide are produced in equal amounts. So why is c-peptide testing preferable to insulin as a guide to beta cell function? The degradation rate of c-peptide in the body is slower than that of insulin (half-life of 20–30 min, compared with the half-life of insulin of just 3–5 min), which affords a more stable test window of fluctuating beta cell response. In healthy individuals the plasma concentration of c-peptide in the fasting state is 0.3–0.6 nmol/l, with a postprandial increase to 1–3 nmol/l **(8)**.

A low level of C-peptide may be considered normal if blood sugar is low and haven't eaten recently. It can also mean that body isn't making enough insulin or that taking insulin injections. This can be related to one of the following medical conditions, type 1 diabetes, type 2 diabetes. Low C-peptide also might indicate that diabetes treatment isn't working well enough. Other medical conditions that can cause low C-peptide with low blood sugar levels include, Addison disease, a disorder in which adrenal glands make too little of the hormones cortisol and aldosterone, this is usually accompanied with a low blood sugar result, liver disease and insulin administration by injection/inhalation (exogenous insulin) **(9)**.

A high level of C-peptide might mean the body is making too much insulin. That can point to one of the following medical conditions, Cushing syndrome (increased secretion of cortisol hormone), insulin resistance, low levels of potassium in the blood (hypokalemia), type 2 diabetes, pancreatic tumor (insulinoma) and kidney failure **(10)**.

Potential problems with C-peptide measurement

The majority of c-peptide is metabolized by the kidneys with 5–10% then excreted unchanged in the urine. This can make c-peptide measurement in individuals with chronic kidney disease inaccurate. It should be noted that c-peptide will be expressed in nanomoles per liter in this article, as opposed to picomoles per milliliter, picomoles per liter, or nanograms per milliliter, which are often quoted in the literature (1 nmol/l = 1 pmol/ml = 1000 pmol/l = 3 ng/ml) **(11)**.

Methods of collection of C-peptide

Various methods of c-peptide estimation have been advocated. Urinary c-peptide (UCP) is a non-invasive test, which can be performed in an outpatient setting. When collected in boric acid UCP is stable at room temperature for up to 3 days. In patients with normal renal function, UCP quantity is reflective of 5–10% of total c-peptide secreted by the pancreas. The 24 h urinary c-peptide sample collection (24 h UCP) is a more time-consuming method, which is inconvenient for the patient, making it a less attractive option than spot UCP. In subjects with normal glucose tolerance urinary c-peptide to creatinine ratio (UCPCR) has been shown to correlate well with 24 h urinary c-peptide **(12)**.

Venous blood c-peptide levels can be measured in the random, fasting, or stimulated state. Random samples are taken at any time during the day without consideration of recent food intake, whereas fasting samples are taken after an 8- to 10-h fast. Stimulation methods include using glucagon, intravenous/oral glucose, tolbutamide, sulfonylurea, and glucose-like peptide 1, amino acids, or a mixed meal. Random non-fasting sampling (rCP) is the simplest method allowing flexibility to test in an outpatient or inpatient setting. rCP has been shown to correlate with fasting c-peptide (fCP) and post glucagon stimulation test (GST) samples in subjects with well-defined type 1 or type 2 diabetes. Similarly, rCP has been shown to correlate with 90 min mixed meal tolerance test (MMTT) c-peptide responses **(13)**.

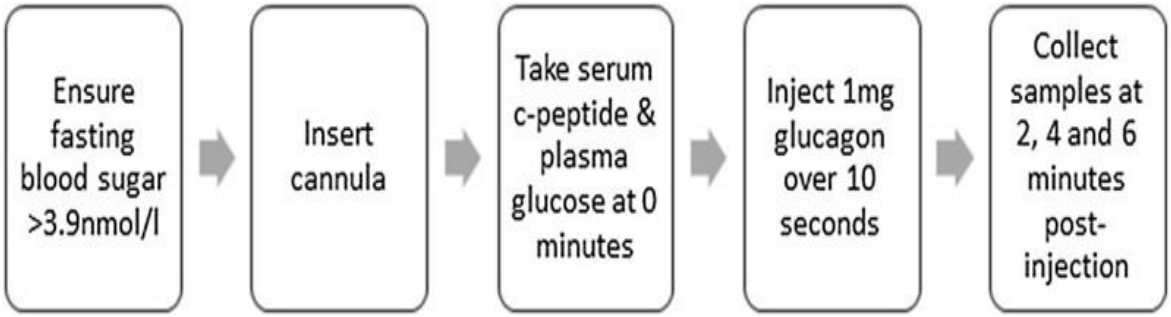

Figure 1: Glucagon-stimulated c-peptide test (GST) 14)

Role in diagnosis and diabetes classification

C-peptide has been shown to denote endogenous insulin production and correlates with type of disease, duration of diabetes, as well as age of diagnosis. The various practical applications of c-peptide measurement **14)**

In insulin-treated individuals, fCP less than 0.2 nmol/l and GST of less than 0.32 nmol/l have been found to correlate significantly with T1DM, with greater sensitivity and specificity than urinary testing **(5)**.

Table 1: Indications for c-peptide measurement (14)

Diagnostic
• **To define T1DM**
• **Criteria for acceptance for CSII**
• **To determine whether T1DM or T2DM**
• **Diagnostic test for MODY**
• **Diagnostic test for LADA, in addition to antibody testing**
Prognostic
• **Marker of duration of diabetes**
• **Lower levels are associated with microvascular complication risk in T1DM**
• **Associated with glycemic variability/HbA1C level**
• **Lower levels are associated with greater hypoglycemia risk**
Therapeutic response
• **Lower baseline levels associated with increased need for insulin**
• **Lower baseline levels associated with shorter time to insulin treatment**
• **Higher levels present in patients who respond to metformin and glibenclamide in combination**
• **Higher levels associated with response to thiazolidinediones**
• **Correlates with reduction in HbA1C following initiation of GLP-1 agonist therapy**

CSII: continuous subcutaneous insulin infusion, MODY: maturity-onset diabetes of the young, LADA: latent autoimmune diabetes of adults

The diabetes control and complications trial (DCCT) was the landmark study which helped generate the targets we presently use for T1DM. Entry to the DCCT required individuals to have insulin-dependent diabetes mellitus of at least 5 years' duration with a baseline mixed meal stimulated c-peptide of less than 0.2 nmol/l. Later in the study, entry criteria were extended to include those with a baseline mixed meal stimulated c-peptide of up to 0.5 nmol/l. The study determined that intensive treatment with three or more insulin injections or continuous subcutaneous insulin infusion (CSII) therapy reduces the incidence of microvascular complications and the later follow-up of the cohort showed a reduction in adverse

cardiovascular outcomes. C-peptide concentration has been shown to decline over decades with duration of diabetes. DCCT data obtained at screening to enter the study showed that diabetes duration was associated with c-peptide value; 48% of individuals with T1DM of up to 5 years' duration had a mixed meal stimulated c-peptide of at least 0.2 nmol/l (corresponding with preserved beta cell function), but only 8% of those with diabetes duration 5–15 years had a stimulated c-peptide of at least 0.2 nmol/l **(15)**

It was confirmed that c-peptide declines over time and is significantly related to age of onset with a younger age of onset (less than 10 years) resulting in a far more rapid c-peptide decline. A higher percentage of detectable c-peptide has been found in those with T1DM aged older than 18 years, compared to those younger than 18 years. The "Diabetes Diagnostics" app has been created by the University of Exeter diabetes research team as a convenient resource for the diagnosis of MODY and other types of diabetes on the basis of clinical criteria according to national and international guidelines in addition to c-peptide interpretation **(16)**.

C-peptide is a useful tool in the classification of diabetes. It can help differentiate T1DM, T2DM, and MODY. C-peptide is associated with duration of disease as well as age of diagnosis. Whilst c-peptide is useful in classifying diabetes it must always be interpreted in clinical context of disease duration, comorbidities, and family history **(16)**.

Prediction of need for insulin

There is limited evidence in the literature about whether c-peptide can effectively predict whether patients require insulin. A peak GST c-peptide of less than 0.6 nmol/l was determined to be associated with later treatment with insulin. Additionally, it was found that a median fasting c-peptide concentration at diagnosis was lower in patients immediately treated with insulin (0.24 nmol/l, range 0.10–1.54) compared with those managed initially with diet with or without oral therapy (0.73 nmol/l, range 0.10–4.10). The fCP of less than 0.25 nmol/l at diagnosis as an independent factor had 60% sensitivity and 96% specificity for association with insulin treatment at follow-up. Islet cell antibody (ICA) positivity in combination with low fCP was found to significantly correlate with future insulin treatment **(17)**.

Time to insulin treatment may also be associated with c-peptide response. In insulin-treated individuals with T2DM, it was reported that time to insulin prescription in individuals with an MMTT c-peptide of at most 0.2 nmol/l (suggesting absolute insulin deficiency) was 2.5 (1.5–3) years compared to 6 (3–10.75) years for those with a mixed meal stimulated c-peptide of greater than 0.2 nmol/l. The ability of c-peptide estimation to confirm the appropriateness of intensive insulin treatment has been practically applied in some healthcare systems such as being used as a criterion for determining if an individual with diabetes is a suitable candidate for CSII therapy. A stimulated c-peptide concentration of at most 0.2 nmol/l may be used as a cutoff value predictive of poor beta cell reserve and likely requirement of insulin therapy, for which intensive therapy has been shown to be efficacious. Additionally, a fasting c-peptide value less than 0.25 nmol/l, alone or especially if in combination with ICA positivity, is a useful test for determining likely future insulin treatment **(18)**.

Prediction of response to non-insulin therapies in T2DM

There is variable evidence to support the use of c-peptide to predict response to non-insulin treatments for T2DM. Higher MMTT stimulated c-peptide has been shown to be present in patients who respond to metformin and glibenclamide in combination, but GST c-peptide did not predict response to glibenclamide alone. High fCP is associated with response to the thiazolidinediones, rosiglitazone and pioglitazone, which is in keeping with their action of reducing insulin resistance. Whilst cohort studies of mixed DPP4 inhibitor use has shown that initial higher fCP predicts reduction of HbA1c, this association was not found in sitagliptin use in addition to metformin or a sulfonylurea **(19)**.

Role of C-peptide in prediction of complications of diabetes

An area of growing research is the question as to whether c-peptide can be used to predict diabetes complications. Lower c-peptide values have been associated with poorer glycemic control and hence increased HbA1c values **(20)**.

The correlation between c-peptide and clinical outcomes in insulin-dependent diabetes was previously reported. Uniformly in the "intensive" treatment group higher and sustained levels of c-peptide (i.e., greater

than 0.2 nmol/l consistently) were associated with reduced incidence of retinopathy and nephropathy. The risk reduction of retinopathy between "non-responder" (c-peptide less than 0.2 nmol/l) and "responder"(c-peptide 0.2–0.5 nmol/l) groups was 58%, and for sustained retinopathy the risk reduction was even higher at 79%. C-peptide also downregulates the expression of several hyperglycemia-induced adhesion molecules, including vascular cellular adhesion molecule 1 (VCAM1), reducing leukocyte adhesion to endothelial cell walls and preventing the early stages of atherosclerosis plaque formation. It was demonstrated that giving subcutaneous c-peptide alongside insulin to individuals with T1DM may ameliorate microvascular complications, such as albuminuria and autonomic nerve dysfunction **(21)**.

Higher levels of c-peptide have consistently been shown to be associated with cardiovascular and all-cause mortality in people without diabetes. This is presumably because raised c-peptide levels are a marker of insulin resistance and metabolic syndrome phenotype. It seems that c-peptide is associated with increasing microvascular complications when low and macrovascular complications when high, which may make interpretation of results difficult when attempting to predict outcomes in clinical practice **(22)**.

Guidelines

Despite studies showing the potential importance of c-peptide as a marker in the diagnosis and of outcomes in diabetes, current national and international guidelines do not advocate its use. According to the American Diabetes Association (ADA) guidelines, the role of c-peptide in the diagnosis of diabetes is currently limited to unusual or ambiguous cases of T1 or T2DM. C-peptide is still felt to be a more important tool in research rather than in day-to-day clinical practice. An ADA-sponsored workshop in 2001 concluded unanimously that c-peptide estimation be used as the most appropriate outcome measure for preservation of beta cell function **(23)**.

In recent guidelines developed by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), documenting the levels of c-peptide is recommended when there is doubt over the diagnosis T1 or T2DM. A recent systematic review supported the diagnostic utility of c-peptide, recommending its use as the principal baseline measure of insulin deficiency. Given the evidence, that c-peptide estimation may in future have a more prominent role in guidelines relating to diagnosis and management of diabetes **(24)**.

Potential future uses

Potential future uses of c-peptide are broad including aiding appropriate diagnosis, guiding therapy choices, and predicting morbidity in diabetes. Stimulated c-peptide sampling is a sensitive and specific test, which can help determine type and duration of diabetes. With many previous studies including small numbers and using fasting c-peptide, future work could include prospective design, larger patient populations, and use stimulated c-peptide as a more accurate parameter **(25)**.

Furthermore, evidence is currently limited with respect to predicting rarer forms of primary diabetes, such as MODY or LADA. In time, c-peptide may become a screening tool to reduce need for autoantibody tests being performed in certain patients to confirm or exclude a diagnosis. A lower c-peptide, specifically less than 0.2 nmol/l, can most likely predict requirement for insulin. Lower c-peptide values have been shown to correspond with increased incidence of microvascular complications. It would be interesting to determine whether c-peptide concentrations are associated with increased macrovascular morbidity and mortality **(26)**.

Umbilical cord C-peptide levels in IDM

Despite marked declines in neonatal mortality nowadays, diabetes mellitus (DM) with pregnancy either gestational (GDM), type 1, or 2 is still associated with a risk of maternal, fetal, and neonatal morbidities and mortalities. Moreover, its prevalence did not decline, as GDM was about 8.74%. Infants of a diabetic mother (IDM) often have complications closely linked to fetal hyperglycemia and hyperinsulinemia, induced by maternal hyperglycemia. In the first trimester, maternal hyperglycemia can cause spontaneous abortions or major birth defects such as truncus arteriosus or aortic coarctation. In the second and third trimesters, maternal hyperglycemia can cause fetal hyperglycemia and hyperinsulinemia, which lead to post-natal

neonatal hypoglycemia, hypocalcemia, polycythemia, hyperbilirubinemia, septal myocardial hypertrophy, delayed lung maturation, and macrosomia **(27)**.

Most IDMs develop asymptomatic hypoglycemia in the first postnatal hours, as after delivery, the transplacental supply of high glucose is stopped. Hyperinsulinemic hypoglycemia is a major risk factor for brain injury and subsequent neurodevelopmental impairments; therefore, rapid identification and prompt management of the newborn with hypoglycemia are essential to avoid brain damage. In this context, early detection of babies at high risk of hypoglycemia is important. Human C-peptide is a 31-amino acid chain secreted from the beta cells of the pancreas in equimolar ratio with the insulin level. It was chosen over insulin to estimate neonatal hyperinsulinemia, as C-peptide has a long half-life and is unaffected by several blood processing conditions such as hemolysis **(28)**.

Human C-peptide is part of the insulin precursor molecule. It is necessary for the correct folding of insulin amino acid chains to their final form and is secreted in equimolar concentrations with insulin. Any process affecting insulin secretion could also affect C-peptide concentration; as a result, it might be considered a proxy variable reflecting metabolic alterations. Due to the detrimental feto-maternal impact of metabolic aberrations on the gravida and her child, growing attention to the correlation between these aberrations and cord blood C-peptide concentration has emerged in recent years **(29)**.

Maternal metabolic aberrations increase the likelihood of gestational disturbances, adverse neonatal outcomes, childhood disorders of glucose metabolism, and childhood obesity. The effect of metabolic aberrations on the fetus could lead to long-term consequences, including diabetes, hypertension, obesity, cardiovascular dysfunction, and metabolic syndrome. Simultaneously, these aberrations might be correlated with the concentration of maternal and cord blood circulating analytes. This has rendered cord blood C-peptide concentration a potential complementing marker reflecting the status of feto-maternal metabolism. For instance, maternal obesity and excessive gestational weight gain (GWG) contribute to increased maternal insulin secretion, elevated risk of developing GDM, and possibly increased cord blood insulin and C-peptide concentration. Moreover, increased maternal plasma glucose might trigger fetal pancreas hypertrophy -a prerequisite for fetal macrosomia and hyperinsulinemia- and might increase cord blood insulin and C-peptide concentration (**30)**.

C-peptide concentration does offer potential as a marker to indicate childhood metabolic outcomes. Moreover, C-peptide concentration measurement might improve risk stratification in neonates born to overweight or diabetic mothers, allowing appropriate resource allocation to those most at risk. Prior research has tried to bring this matter into the light, as it has investigated the association between C-peptide concentration and maternal BMI, diabetes, GWG, and fetal overgrowth **(31)**.

Maternal control during pregnancy mainly depends on diet and insulin control. The degree of control can be increased by serial measurements of blood glucose (BG) and glycated hemoglobin (HbA1C). However, HbA1C, now the current gold standard marker for glycemic control, reflects the BG level over the previous 2–3 months. It is a strong predictor of diabetic complications, and the cut-off used is 6.5% to diagnose diabetes. It was reported that poor diabetes control, especially in the last trimester, is associated with neonatal hypoglycemia. Furthermore, increased UC C-peptide levels could be used as an early indicator for risk of developing neonatal hypoglycemia and a predictor for babies need neonatal admission. Major risk factors for developing GDM during pregnancy include increased maternal age, a family history of diabetes, a history of GDM in a previous pregnancy, a history of macrosomia in a previous pregnancy, and an increased pre-gravid body mass index **(32)**.

In a population-based cohort study performed in different geographical regions, it was demonstrated that UC blood concentration of C-peptide is significantly associated with the incidence of maternal GDM and neonatal macrosomia. Measuring C-peptide concentration has the potential to improve the risk stratification of neonates born to overweight or diabetic mothers. Though it seems promising, the existing evidence supporting the link between UC blood C-peptide concentration and feto-maternal metabolic outcomes is not yet adequate **(31)**.

References:

1. Grev, J. E., Munger, K. M. & Scott, S. M. 2020. Infant of a Diabetic Mother. S D Med, 73, 323-7.
2. Lemaitre, M., Ternynck, C., Bourry, J., et al. 2022. Association Between HbA1c Levels on Adverse Pregnancy Outcomes During Pregnancy in Patients With Type 1 Diabetes. J Clin Endocrinol Metab, 107, 1117-25.
3. Oxman, R., Roe, A. H., Jagdeesh, U., et al. 2022. Gestational and pregestational diabetes in pregnant women with cystic fibrosis. J Clin Transl Endocrinol, 27, 100-8.
4. Yosten, G. L., Maric-Bilkan, C., Luppi, P., et al. 2014. Physiological effects and therapeutic potential of proinsulin C-peptide. Am J Physiol Endocrinol Metab, 307, 955-68.
5. Maddaloni, E., Bolli, G. B., Frier, B. M., et al. 2022. C-peptide determination in the diagnosis of type of diabetes and its management: A clinical perspective. Diabetes ObesMetab, 24, 1912-26.
6. Landreh, M. &Jörnvall, H. 2021. Biological activity versus physiological function of proinsulin C-peptide. Cell Mol Life Sci, 78, 1131-8.
7. Essid, S. M., Bevington, A. & Brunskill, N. J. 2019. Proinsulin C-Peptide Enhances Cell Survival and Protects against Simvastatin-Induced Myotoxicity in L6 Rat Myoblasts. Int J Mol Sci, 20, 70-8.
8. Elzahar, W., Arafa, A., Youssef, A., et al. 2020. Urinary C-peptide creatinine ratio to differentiate type 2 diabetes mellitus from type 1 in pediatric patients. Eur J Pediatr, 179, 1115-20.
9. Sørgjerd, E. P., Åsvold, B. O. & Grill, V. 2021. Low C-peptide together with a high glutamic acid decarboxylase autoantibody level predicts progression to insulin dependence in latent autoimmune diabetes in adults: The HUNT study. Diabetes ObesMetab, 23, 2539-50.
10. Rickels, M. R., Evans-Molina, C., Bahnson, H. T., et al. 2020. High residual C-peptide likely contributes to glycemic control in type 1 diabetes. J Clin Invest, 130, 1850-62.
11. Hörber, S., Orth, M., Fritsche, A., et al. 2023. Comparability of C-Peptide Measurements - Current Status and Clinical Relevance. Exp Clin Endocrinol Diabetes, 131, 173-8.
12. Hope, S., Knight, B. A., Shields, B. M., et al. 2016. Low c-peptide is associated with high glycaemic variability and hypoglycaemia in insulin-treated patients with type 2 diabetes. Diabet Med, 33, 18-23.
13. Sonoda, R., Tanaka, K., Kikuchi, T., et al. 2016. C-Peptide Level in Fasting Plasma and Pooled Urine Predicts HbA1c after Hospitalization in Patients with Type 2 Diabetes Mellitus. PLoS One, 11, 147-55.
14. Leighton, E., Sainsbury, C. A. & Jones, G. C. 2017. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther, 8, 475-87.
15. Hao, W., Gitelman, S., DiMeglio, L. A., et al. 2016. Fall in C-Peptide During First 4 Years From Diagnosis of Type 1 Diabetes: Variable Relation to Age, HbA1c, and Insulin Dose. Diabetes Care, 39, 1664-70.
16. Colclough, K. & Patel, K. 2022. How do I diagnose Maturity Onset Diabetes of the Young in my patients? Clin Endocrinol (Oxf), 97, 436-47.
17. Wei, Y., Quan, L., Zhou, T., et al. 2021. The relationship between different C-peptide level and insulin dose of insulin pump. Nutr Diabetes, 11, 7-11.
18. Iqbal, S., Jayyab, A. A., Alrashdi, A. M., et al. 2023. The Predictive Ability of C-Peptide in Distinguishing Type 1 Diabetes From Type 2 Diabetes: A Systematic Review and Meta-Analysis. Endocrine Practice, 29, 379-87.
19. Demir, S., Temizkan, S. & Sargin, M. 2016. C-Peptide Levels Predict the Effectiveness of Dipeptidyl Peptidase-4 Inhibitor Therapy. J Diabetes Res, 2016, 45-8.
20. Lachin, J. M., McGee, P. & Palmer, J. P. 2014. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes, 63, 739-48.
21. Williams, K. V., Becker, D. J., Orchard, T. J., et al. 2019. Persistent C-peptide levels and microvascular complications in childhood onset type 1 diabetes of long duration. J Diabetes Complications, 33, 657-61.
22. Pikkemaat, M., Melander, O., Mölstad, S., et al. 2015. C-peptide concentration, mortality and vascular complications in people with Type 2 diabetes. The Skaraborg Diabetes Register. Diabet Med, 32, 85-9.
23. Buzzetti, R., Tuomi, T., Mauricio, D., et al. 2020. Management of Latent Autoimmune Diabetes in Adults: A Consensus Statement From an International Expert Panel. Diabetes, 69, 2037-47.
24. Shields, B. M., Peters, J. L., Cooper, C., et al. 2015. Can clinical features be used to differentiate type 1 from type 2 diabetes? A systematic review of the literature. BMJ Open, 5, 90-8.
25. Zashikhina, N., Sharoyko, V., Antipchik, M., et al. 2019. Novel Formulations of C-Peptide with Long-Acting Therapeutic Potential for Treatment of Diabetic Complications. Pharmaceutics, 11, 70-8.
26. Peixoto-Barbosa, R., Reis, A. F. & Giuffrida, F. M. A. 2020. Update on clinical screening of maturity-onset diabetes of the young (MODY). DiabetolMetab Syndr 12, 50-8.
27. Tsakiridis, I., Giouleka, S., Mamopoulos, A., et al. 2021. Diagnosis and Management of Gestational Diabetes Mellitus: An Overview of National and International Guidelines. ObstetGynecolSurv, 76, 367-81.
28. Wu, Z. Q., Lu, J. & Xu, H. G. 2016. Hemolysis Affects C-Peptide Immunoassay. J Clin Lab Anal, 30, 1232-5.

29. ÖzbörüAşkan, Ö., Bozaykut, A., Sezer, R. G., et al. 2015. Effect of Maternal Factors and Fetomaternal Glucose Homeostasis on Birth Weight and Postnatal Growth. J Clin Res Pediatr Endocrinol, 7, 168-74.
30. Lindsay, K. L., Brennan, L., Rath, A., et al. 2018. Gestational weight gain in obese pregnancy: impact on maternal and foetal metabolic parameters and birthweight. J ObstetGynaecol, 38, 60-5.
31. Niknam, A., Ramezani Tehrani, F., Behboudi-Gandevani, S., et al. 2022. Umbilical cord blood concentration of connecting peptide (C-peptide) and pregnancy outcomes. BMC Pregnancy Childbirth, 22, 764-9.
32. Saber, A. M., Mohamed, M. A., Sadek, A. A., et al. 2021. Role of umbilical cord C-peptide levels in early prediction of hypoglycemia in infants of diabetic mothers. BMC Pediatr 21, 85-92.