Department of Biochemistry

Newsletter

All India Institute of Medical Sciences,Rajkot

CLINIAL BIOCHEMISTRY & MOLECULAR BIOLOGY BULLETIN

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This issue is dedicated to

DIABETES MELLITUS TYPE I

HIP- A NEW PLAYER IDENTIFIED IN TI-DM

Hybrid Insulin Peptides (HIPs) are PROTEINS found on beta-cells of people with TI-DM & are recognized as foreign by their immune cells.

Type 1 diabetes is caused by an autoimmune attack of insulin-producing beta-cells, mediated by T-cells.

The strongest genetic risk for developing T1D is associated with the **HLA class II haplotypes** HLA-DR3-DQ2 (Odds ratio (OR)>3.6) and HLA-DR4-DQ8 (OR>11.37)
The second known cause is said to be that **proinsulin-specific CD4+ T cells** infiltrate human islets in type 1 diabetes. Human islet-infiltrating CD4+ T cells recognize several epitopes derived from the C-peptide presented by HLA-DQ8 or DQ8trans

An important twist in proinsulin's role in T1D came in 2016 when researchers described **hybrid insulin peptides (HIPs)** which is a CD4+ T-cell epitope that is formed by the posttranslational fusion of two peptide fragments. As the name suggests, at least one of the peptide fragments derives from insulin or proinsulin.

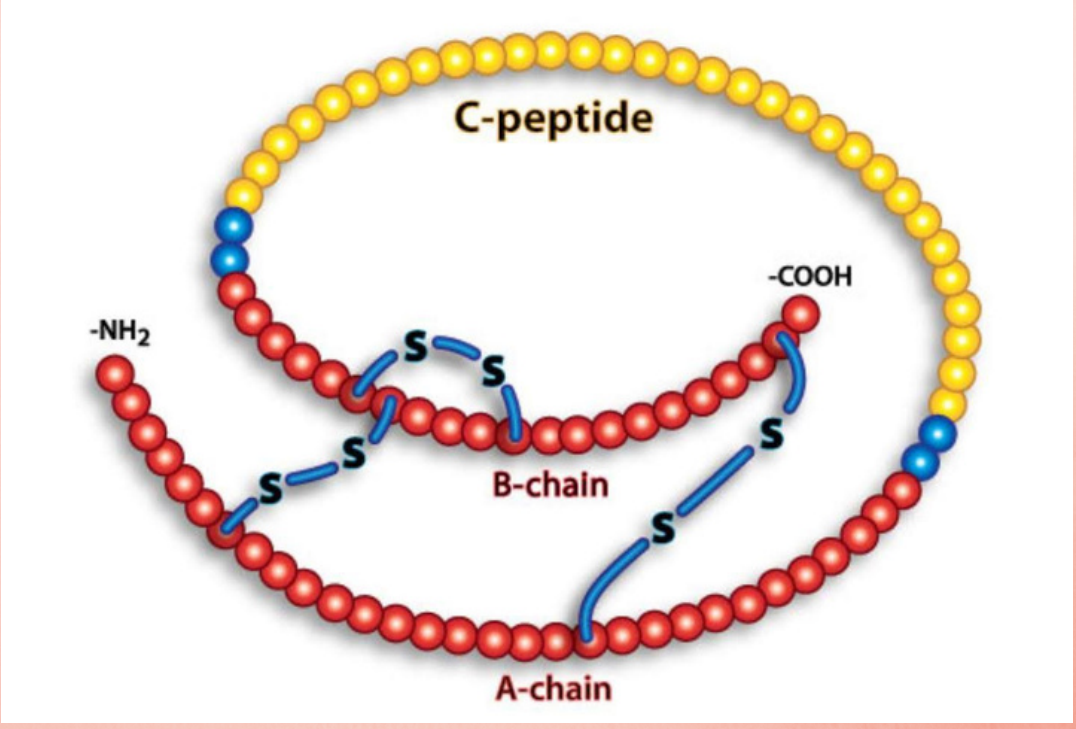
An epitope from the beta-cell secretory granule protein, **chromogranin-A (ChgA)** is suspected to be, a partial target for a family of T-cell clones, known as BDC, specifically BDC-2.5 & BDC-6.9

How do HIPs Form?

Beta-cell granules are extremely densely packed with insulin, C-peptide, and several other proteins including chromogranins and amyloid proteins. Furthermore, the beta-cell granules are the site of very active proteolysis. Many proteins found in the beta cell granules, including proinsulin (PI), chromogranins (Chg), and islet amyloid polypeptide (IAPP), are cleaved by the granule proteases to generate an array of bio-active peptides.
Analysis of mass spectrometry data from beta-cell crinosomes revealed the presence of HIPs suggesting that HIPs form in the crinosomes when the appropriate peptides are digested by the lysosomal protease, cathepsin L, HIPs that activate the lines **BDC-2.5 and BDC-6.9** are generated. This led to the suggestion that HIPs form when senescent insulin granules fuse with lysosomes to form crinophagic granules.

The high concentration of insulin granule proteins and cathepsin-L favors the formation of HIPs. Crinophagic granules can be taken up by antigen-presenting cells allowing the HIPs to be presented to CD4+ T cells

Nonetheless, the precise location(s) of HIP formation remain unclear. C-peptide can be cleaved at sites other than the dibasic residues at the B-C and C-A chain junctions. This indicates that other proteases may mediate the formation of HIPs. It also remains possible that transpeptidation and HIP formation occurs in both granules and crinosomes.



What's New!!!!

The bionic pancreas improves type 1 diabetes management compared to standard insulin delivery methods.

Next-generation technology maintains blood glucose levels by automatically delivering insulin.

A device known as a bionic pancreas, which uses next-generation technology to automatically deliver insulin, was found to be more effective at maintaining blood glucose (sugar) levels within normal range than standard-of-care management among people with type 1 diabetes, a new multicenter clinical trial has found. The trial was primarily funded by the **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part** of the National Institutes of Health, and published in the New England Journal of Medicine

Dasiglucagon, a new human Glucagon Analog Peptide

Newly discovered Dasiglucagon is the leading glucagon medication available in a prefilled syringe or autoinjector as a liquid preparation, developed by Zealand Pharma.
Dasiglucagon was approved for the first time by the United States Food and Drug Administration (USFDA) in March 2021 to treat severe hypoglycemia in pediatric and adult diabetic patients

Tid-Bits From History

The Discovery of Cori's Cycle

Gerty Cori, & her husband **Carl Ferdinand Cori,** Biochemists, received Nobel Prize in Physiology or Medicine in the year 1947 for their significant role in the "discovery of the course of the catalytic conversion of glycogen".

Gerty Cori became the **third woman—and the first American woman—to win a Nobel Prize in science, & the first woman to be awarded the Nobel Prize in Physiology or Medicine.** They discovered the mechanism by which glycogen is broken down in muscle tissue into lactic acid and then resynthesized in the body and stored as a source of energy (known as the Cori cycle).

They also identified the important catalyzing compound, Glucose-1-Phosphate, the Cori ester. The Coris were the third-ever married couple to win the Nobel Prize.

FUNFACT

Early Discovery of Diabetes

Fact #1: The ancient Egyptians mentioned the symptoms of diabetes in manuscripts that date back to 1500 B.C.

Fact #2: In India, physicians used to refer to diabetes as madhumeha, which translates to 'honey urine' since the urine of people with diabetes attracted ants. In fact, to test for diabetes, physicians would analyze urine to see if sugar-loving ants would come to the urine. Today, we know this occurs because extra sugar is expelled from the body through the urine.

Fact #3: In the 2nd Century AD Aretaeus, a great physician during the Greco-Roman period, officially introduced the term diabetes. The word diabetes comes from the Greek word διαβαινω (diabaino), which means "I pass through".

Fact #4: It wasn't until the 1600s that the term 'Mellitus' came around. English physician and anatomist Thomas Willis wrote about the sweetness of urine among those with diabetes, which he referred to as the "pissing evil." Eventually, he came up with the term 'Mellitus'.

The Accomplishment Corner

Association of Clinical Biochemists of India (ACBI), 48th National Conference

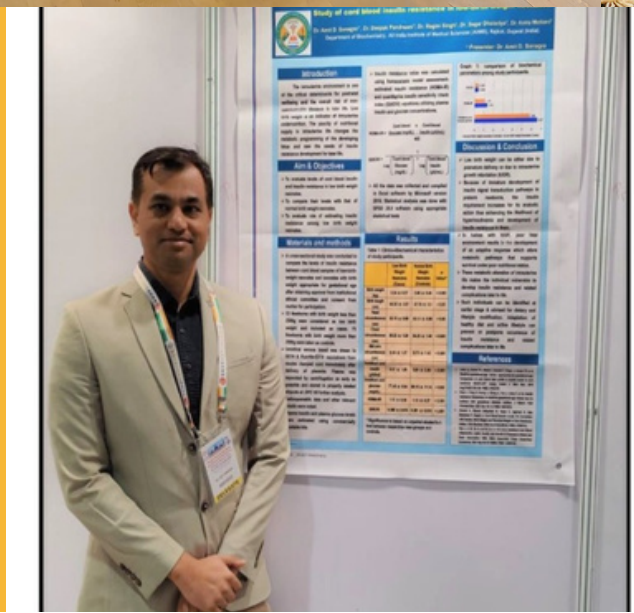
Held at New Delhi, from 24th-26th November, 2022

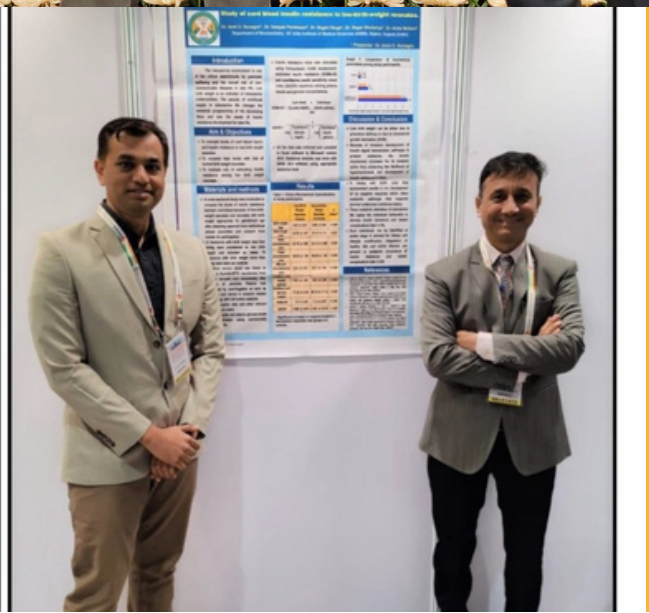
Dr. Deepak Parchwani, Additional Professor & Head, Department of Biochemistry conveyed a symposium talk on **'Inflammatory Cytokines in Diabetic Nephropathy'** and was acknowledged, felicitated by ACBI & IFCC (International federation of clinical chemistry) for his contribution in the field of Clinical Biochemistry.

Dr. Amit Sonagra, Assistant Professor presented a poster in the category of **"Endocrinology and Metabolism".**

Both the presenters proudly represented the Department of Biochemistry, AIIMS Rajkot, on a National level.

A Glimpse of the event





Title of the article: Inflammatory cytokines in diabetic nephropathy.

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Abstract

Preceding clinical studies and analysis in animal models has ascertained the low-grade inflammation to be involved in the pathogenetic processes in the development of diabetic nephropathy (DN). Mediators of inflammation such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6 and IL-8 are forerunners for the development of diabetic complications. Thus, this study is aimed to assess the serum levels of TNF-α, IL-1, IL-6 and IL-8 among the diabetic nephropathy patients to ascertains its role. Pre-diagnosed diabetic patients were recruited for the study. All recruited patients were screened for renal complication due to diabetes and thus were asked to collect a three urine samples, in space of at least 6 months apart for analysis of albumin excretion rate (AER). Urine collection was carried out during unrestricted daily life activity and was tested for AER by immunoturbidimetric assay (CV %: 3.2). The patients were divided into two groups depending on the absence (AER\30 mg/day and not treated with ACE inhibitors or angiotensin receptor blockers) or presence of nephropathy (AER [300 mg/day) in at least two of the three collections. Microalbuminuric patients (AER 30–299 mg/day) were not retained because they could not be surely classified as case patients or controls. A statistically significant difference between cases and control groups as regard to serum TNF-α, IL-1, IL-6 and IL-8 ($p<0.05$) were observed. Atypical levels of TNF-α, IL-1, IL-6 and IL-8 in patients with diabetic nephropathy support a possible role for inflammation in diabetic microvascular complications.

Key Words: Diabetic Nephropathy, Tumor Necrosis Factor-alpha TNF-α, Interleukin -1, Interleukin -6 and Interleukin -8

Title: Study of cord blood insulin resistance in low-birth-weight neonates.

Authors: Dr. Amit D. Sonagra, Dr. Deepak Parchwani, Dr. Ragini Singh, Dr. Sagar Dholariya, Dr. Anita Motiani.

All the authors are affiliated to: Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Rajkot, Gujarat, India.

Presenter: Dr. Amit D. Sonagra
ACBI Life membership No.: 3903/LM/JOUR

Abstract

The intrauterine environment is one of the critical determinants for postnatal wellbeing and the overall risk of non-communicable diseases in later life. Low birth weight is an indicator of intrauterine undernutrition. The paucity of nutritional supply in intrauterine life changes the metabolic programming of the developing fetus and saw the seeds of insulin resistance development for later life. A cross-sectional study was conducted to compare the levels of insulin resistance between cord blood samples of low-birth-weight neonates and neonates with birth weight appropriate for gestational age. Plasma insulin and plasma glucose levels were estimated from the cord blood samples of 33 low-birth-weight neonates (cases) and 70 normal birth weight neonates (controls). Insulin resistance value was calculated using homeostasis model assessment-estimated insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) equations utilizing plasma insulin and glucose concentrations. We observed significantly higher values of HOMA-IR (1.33 ± 0.30 vs 1.12 ± 0.27) and significantly lower values of QUICKI (0.368 ± 0.015 vs 0.381 ± 0.016) in low-birth-weight neonates compared to neonates with normal birth weight ($p<0.05$) which denotes higher level of insulin resistance in low-birth-weight neonates. Such neonates are at a higher risk of developing insulin resistance and its consequences in later life. They should be advised to adopt an active lifestyle and a healthy balanced diet. Avoidance of modifiable risk factors can prevent or postpone the occurrence of insulin resistance and related complications.

We are also glad to share recently published Systemic review and meta-analysis on “ **Clinical efficacy and safety of dasiglucagon in severe hypoglycemia associated with patients of type 1 diabetes mellitus: a systematic review and meta-analysis**” in PubMed indexed “ Expert Review of Clinical Pharmacology” journal with IF (4.1) https://pubmed.ncbi.nlm.nih.gov/36266088/

Authors: **Sagar Dholariya, Deepak Parchwani, Siddhartha Dutta & Ragini Singh**

Quote of the day

IF THERE ARE NO UPS AND DOWNS IN YOUR LIFE

IT MEANS YOU ARE DEAD