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Editorial

Dear Members,

Greetings.

Looking forward to welcoming you all to sunny Goa, for the science as well as for the sea and the sand ! The congress organizing committee has lined up some fantastic science for you this October. If you have not booked your tickets for the event of the year, please hurry.

Looking forward to meeting you all in Goa.

Dr. Rajiv R Sinha
General- Secretary,
ACBI & Editor-in-Chief

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Notice for ACBI Meeting

Attention Please! Members of ACBI & ACBI Executive Committee

Please note the dates, timings and Venue of the next EC & GB meetings

Meeting	Date & Time	Venue
Editorial Board of IJCB Meeting	October 24, 2018 3.30 to 4.30 pm	Kala Academy, Panjim
ACBI CW Wing meetings	October 24, 2018 4.30 to 5.30 pm	
Pre GBM EC meeting	October 24, 2018 5.30 to 7.00 pm	
General Body Meeting	October 26, 2018 6.00 to 7.30 pm	Kala Academy, Panjim
Post GBM EC meeting	December 27, 2018 10:00 – 11:30 am	

Note: The timings of the GB & Post GB EC meeting may change as per conference program.

Dr. Rajiv R Sinha
General Secretary, ACBI

NOTICE

We want that all members should actively participate in ACBI activities and be kept informed about the programmes and activities. For this we require your correct addresses and email ID. Please check your details on the ACBI website www.acbindia.org and if any correction is needed, kindly download the **ADDRESS**

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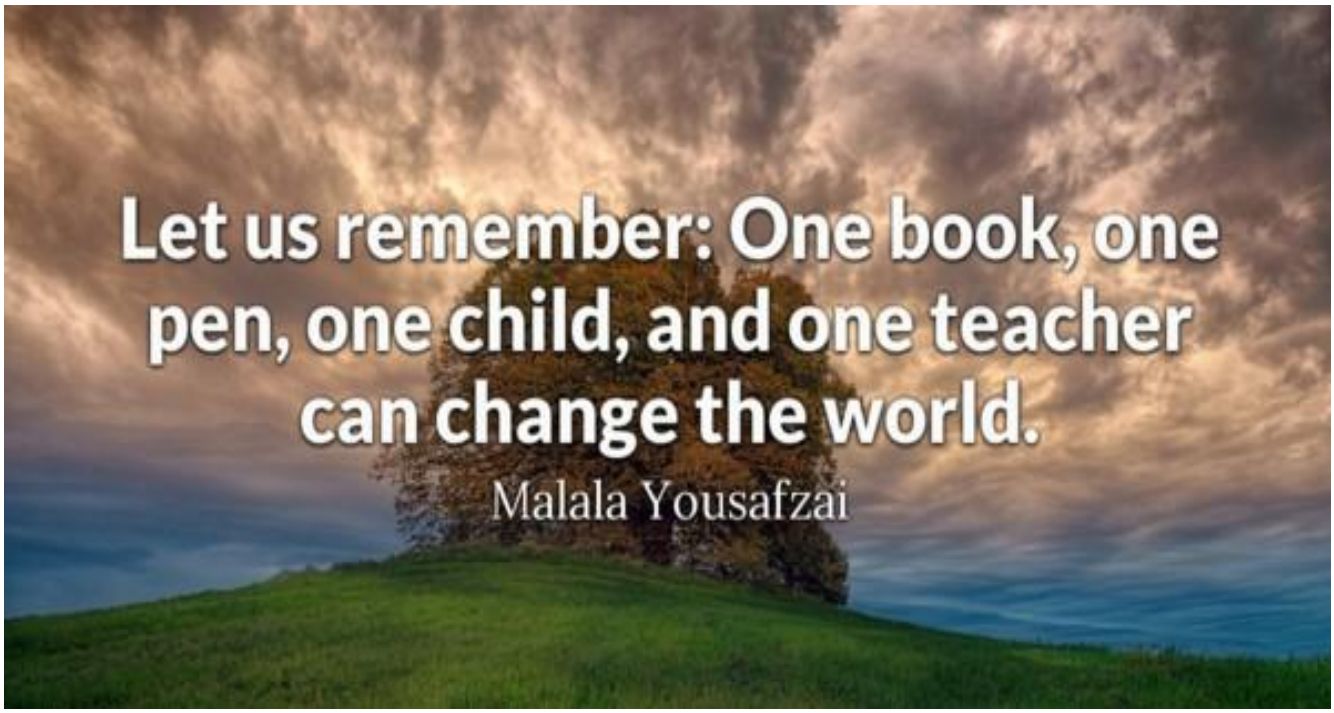

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*Pediatric Metabolic Syndrome: P*athophysiology and laboratory assessment

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ABSRACT

Pediatric overweight and obesity is an emerging public health priority as rates have rapidly increased worldwide. Obesity is often clustered with other metabolic abnormalities including hypertension, dyslipidemia, and insulin resistance, leading to increased risk of cardiovascular disease. This cluster of risk factors, termed the metabolic syndrome, has traditionally been reported in adults. However, with the increased prevalence of pediatric obesity, the metabolic syndrome is now evident in children and adolescents. This complex cluster of risk factors is the result of the pathological interplay between several organs including adipose tissue, muscle, liver, and intestine with a common antecedent – insulin resistance. The association of the metabolic syndrome with several systemic alterations that involve numerous organs and tissues adds to the complexity and challenge of diagnosing the metabolic syndrome and identifying useful clinical indicators of the disease. The complex physiology of growing and developing children and adolescents further adds to the difficulties in standardizing laboratory assessment, diagnosis, and prognosis for the diverse pediatric population. However, establishing a consensus definition is critical to identifying and managing children and adolescents at high risk of developing the metabolic syndrome. As a result, the examination of novel metabolic syndrome biomarkers which can detect these metabolic abnormalities early with high specificity and sensitivity in the pediatric population has been of interest. Understanding this complex cluster of risk factors in the pediatric population is critical to ensure that this is not the first generation where children have a shorter life expectancy than their parents. This review will discuss the pathophysiology, consensus definitions and laboratory assessment of pediatric metabolic syndrome as well as potential novel biomarkers.

INTRODUCTION

The worldwide prevalence of pediatric overweight and obesity combined has risen by 47.1% between 1980 and 2013 (1). This alarming increase in pediatric obesity has become a global public health burden, evident by the World Health Organization (WHO) Health Assembly endorsement for the Comprehensive Implementation Plan on Maternal, Infant, and Young Child, Nutrition, which consisted of six global nutrition targets to be achieved by 2025, including "Target 4: no increase in childhood overweight" (2). Obesity is the most important risk factor for cardiovascular disease (CVD) and is often clustered with additional metabolic abnormalities including hypertension, dyslipidemia, and insulin resistance (3). These CVD risk factors tend to cluster, not only in adults, but more recently in children (4). This common cluster of major determinants of CVD led to the definition of what is known as the metabolic syndrome (MetS).

The current paradigm of MetS was established by Reaven and colleagues (5) in 1988, originally termed Syndrome X. Reaven described MetS as the interrelation between insulin resistance, hypertension, type 2 diabetes (T2D), and CVD. Although this syndrome was not defined until the late 1980s, the relationship between obesity, hypertriglyceridemia, and hypertension was first recognized in the early 1980s (6).

This was followed by the description of the central roles of insulin resistance and abdominal obesity in MetS in the late 1980s to early 1990s (7). Clinical definitions of MetS have been extremely variable, however almost all definitions require a partial combination of the following five elements: elevated triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-C), increased blood pressure, elevated fasting plasma glucose, and increased waist circumference (3). Although MetS was once thought to be an adult-onset disease, this clustering of metabolic disorders is becoming increasingly prevalent in children and adolescents, making it a public health priority in the pediatric population as well. This review will discuss what is currently known about the underlying pathophysiology of pediatric MetS, particularly in regards to the major organs involved. Additionally, the difficulty in defining pediatric MetS, current definitions and laboratory assessment to define and monitor pediatric MetS, and potential novel biomarkers will be discussed.

Organization (WHO) predicts that 70 million infants and young children will be overweight or obese by 2025.The prevalence of MetS directly increases with the degree of obesity and each component of the syndrome worsens with increasing obesity, independent of age, sex, and pubertal status (3)

In the Third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994 in the US, the prevalence of MetS in adolescents aged 12-19 years was 4%, increasing to 28.7% among strictly obese adolescents (8). A more recent analysis of NHANES data from 1999-2002, demonstrates that MetS prevalence in obese adolescents has since increased to 44% (9). If current trends continue, the World Health Childhood obesity is also an early risk factor for adult morbidity and mortality (10,11) and 85% of obese children become obese adults (10,12). It is important to detect MetS early in childhood and adolescence to prevent further health complications in adulthood and minimize the global socio-economic burden of CVD and T2D. Unless action is taken, diabetes experts agree that this is the first generation where children may have a shorter life expectancy than their parents (13).

PATHOPHYSIOLOGY: UNDERSTANDING THE COMPLEX CLUSTER

The etiology of MetS is incompletely understood; however, insulin resistance is thought to be central to the development of MetS and play a role in the pathogenesis of its individual metabolic components.

The World Health Organization (WHO) hypothesizes that the association and clustering of T2D, hypertension, dyslipidemia, and CVD arises from a common antecedent - insulin resistance (14). Insulin resistance is the decreased tissue response to insulin-mediated cellular actions.

Although hyperglycemia, the primary complication of insulin resistance, can result in substantial morbidity in T2D, CVD is the leading cause of death in T2D patients, mainly due to lipid abnormalities (15). This phenomenon is well-supported by results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, in which attempts to tightly control glucose did not lead to an improvement in mortality (16,17).

Insulin elicits peripheral effects on several organ systems, including adipose tissue, muscle, liver, and intestine.

Therefore, in insulin resistant states, metabolic dysfunction across several organs occurs, together creating this observed interplay of several concurrent metabolic abnormalities. Lipid partitioning and inflammation.

It is widely accepted that obesity and the concomitant development of inflammation are the major components of insulin resistance (18). In obesity, adipose tissue storage capacity becomes saturated and insulin suppression of adipose tissue lipolysis is diminished (19).

As a result, plasma free fatty acid (FFA) levels increase and this excess lipid can be stored in sites other than conventional subcutaneous adipose depots, including intraabdominal (visceral) adipose compartments and insulin-responsive tissues (i.e. muscle and liver). This altered lipid partitioning can shift the balance between adipocytokines, producing more inflammatory cytokines (i.e. TNF-α and IL-6) and fewer anti-inflammatory peptides (i.e. adiponectin).

In addition to inflammatory effects of obesity, the increased FFA flux results in several metabolic dysfunctions. When the subcutaneous fat depot reaches its storage capacity and lipid is shunted to ectopic tissues (i.e. liver and muscle), peripheral insulin resistance occurs (20). Derivatives of fatty acids (e.g. long chain fatty acyl-CoA and DAG) in hepatocytes and myocytes may alter the insulin signal transduction pathway, leading to this observed decrease in insulin sensitivity. Several studies support this theory, as lipid content in liver and muscle is increased in obese and T2D subjects and is a strong predictor of insulin resistance (21).Furthermore, obese adolescents with a high visceral to subcutaneous fat ratio demonstrate a markedly adverse metabolic phenotype of severe insulin resistance and alterations in glucose and lipid metabolism (22).Taken together, obesity results in increased inflammatory markers and FFA flux, subsequently reducing the insulin sensitivity of several organs (i.e. adipose tissue, muscle, liver, intestine). Insulin resistance across several organs results in the MetS phenotype which includes dyslipidemia, subsequently increasing CVD risk by affecting endothelial function and the vascular system (23).

ADIPOSE TISSUE INSULIN RESISTANCE AND FFA FLUX

Adipose tissue enlargement (i.e. obesity) leads to a proinflammatory state in the cells, with reduced secretion of adiponectin and increased secretion of several inflammatory cytokines and chemokines (24). One of these chemokines, monocyte chemoattractant protein-1 (MCP-1), plays an important role in recruiting macrophages into adipose tissue (24). Macrophages infiltrate adipose tissue and contribute to adipocyte hypertrophy and further cytokine release (24,25). These cytokines can affect insulin action in other tissues, such as liver and muscle, but can also lead to local insulin resistance. Insulin inhibits lipolysis in adipose tissue, and therefore in insulin resistance, lipolysis is accelerated, leading to increased FFA release into the circulation (3). Therefore, insulin resistance further supports the proinflammatory state of obesity because its anti-lipolytic and anti-inflammatory effects are negated.

MUSCLE INSULIN RESISTANCE AND GLUCOSE INTOLERANCE

Increased plasma FFAs, due to reduced insulin suppression of adipose tissue lipolysis, disrupt insulin-mediated glucose uptake by skeletal muscle, facilitating development of hyperglycemia (26). Insulin resistance in skeletal muscle may promote atherogenic dyslipidemia by diverting ingested carbohydrate towards hepatic de novo lipogenesis (DNL), rather than muscle glycogen storage (23).

Young, lean, insulin-sensitive subjects store most of their ingested energy in liver and muscle glycogen, while young, lean insulin-resistant subjects have dysfunctional muscle glycogen synthesis and divert more of their ingested energy into hepatic DNL (27). This results in increased plasma TGs, lower HDL-C, and increased

hepatic TG synthesis (27). Mouse studies further support these findings as muscle-specific inactivation of the insulin receptor gene results in increased plasma TGs and increased adiposity as a result of muscle-specific insulin resistance (28).

HEPATIC INSULIN RESISTANCE AND FASTING DYSLIPIDEMIA

The liver is a main target of insulin action and plays a major role in both carbohydrate and lipid metabolism. Two key hepatic insulin actions are reducing hepatic glucose output and inhibiting secretion of very low-density lipoproteins (VLDLs). To reduce hepatic glucose output, insulin phosphorylates FoxO1, preventing it from entering the nucleus, and consequently reducing the expression of genes required for gluconeogenesis (29). Postprandial insulin release enhances hepatic VLDL production by upregulating lipogenesis via activation of the transcription factor sterol regulatory element-binding protein (SREBP-1c) (30). SREBP-1c increases transcription of genes required for FA and TG biosynthesis, resulting in increased DNL. TGs synthesized by DNL and dietary lipids are packaged with apolipoprotein B100 (apoB100) into VLDLs. Although insulin increases substrate availability for VLDL production, it also acutely reduces VLDL secretion (31). This inhibitory action is thought to be due to an increase in apoB100 degradation, the main structural protein of VLDL (31).

Insulin has key metabolic regulatory roles in the liver, thus several metabolic abnormalities can clinically manifest with hepatic insulin resistance. Diabetic dyslipidemia is one such abnormality which is characterized by hypertriglyceridemia, increased small dense LDL (sdLDL) and decreased HDL-C (32). This phenomenon is the direct result of hepatic insulin resistance which results in impaired glucose homeostasis due to reduced FoxO1-mediated phosphorylation, and enhanced hepatic DNL due to reduced SREBP-1 activation (33). Therefore, both hyperglycemia and hypertriglyceridemia are seen in hepatic in¬sulin resistance. In addition to enhanced DNL, substrates for VLDL synthesis are increased due to elevated FFA flux from adipose tissue and increased hepatic uptake of chylomicron rem-nants (CM; lipoproteins secreted from the in¬testine) and VLDL remnants (34,35).Increased substrate availability for VLDL production and reduced apoB degradation can lead to VLDL overproduction and hypertriglyceridemia. As a result of hypertriglyceridemia, highly atherogenic sdLDL are also produced in insulin resistant states. sdLDL are produced from the action of cholesteryl ester transfer protein (CETP), which exchanges VLDL TG for LDL cholesteryl ester (CE), creating CE-depleted, TG-enriched, LDL particles (36). These particles become sdLDL after they are lipolyzed by lipoprotein lipase (LPL) or hepatic lipase (HL) (36). CETP action is thought to also contribute to reduced HDL-C levels in insulin-resistant subjects (36).

Hepatic steatosis, one of the main detriments to the liver in response to hepatic insulin resistance, is characterized by the accumulation of excess lipid in the liver, which can progress to inflammatory steatohepatitis, fibrosis, and even cirrhosis. This spectrum of diseases is collectively termed non-alcoholic fatty liver disease (NAFLD).Progression of NAFLD can cause liver failure, leading to the need for a liver transplant, even in adolescents (37). As the prevalence of pediatric obesity increases, NAFLD has also increased in prevalence, rapidly becoming the most common cause of pediatric liver disease (37).

Furthermore, a pediatric study showed that every 1 cm increase in waist circumference is associated with a 1.97 and 2.08 fold increased risk of NAFLD in males and females, respectively (34). Although the pathological link between MetS and NAFLD is incompletely understood, the theory of the “two-hit model” is the most widely accepted (38). The first hit is insulin resistance which promotes the accumulation of hepatocyte lipid due to increased hepatic FFAs available for TG synthesis in an insulin resistant state (36).

This results from insulin failing to block adipose tissue lipolysis, resulting in increased FFA release from adipose tissue. Increased circulating FFAs leads to increased FFA uptake by hepatocytes, increased TG synthesis and impaired FFA oxidation, producing excess lipid in hepatocytes (38,39). The second hit is injury from reactive oxygen species (ROS). Lipid accumulation in hepatocytes impairs the oxidative capacity of the mitochondria and can also lead directly to further ROS production (40). Increased susceptibility of hepatocytes to oxidative stress and subsequent lipid peroxidation by ROS promotes progression to nonalcoholic steatohepatitis (NASH). This is due to chemoattractants (i.e. by-products of oxidative stress and lipid peroxidation), which lead to fibrosis and the production of inflammatory cytokines (37).

INTESTINAL INSULIN RESISTANCE AND POSTPRANDIAL DYSLIPIDEMIA

In contrast to the numerous studies on insulin signaling in well-known insulin-sensitive tissues such as liver, muscle, and adipose, relatively little is known regarding intestinal insulin signaling and potential perturbations with insulin resistance (41). The intestine packages absorbed dietary fat into apoB-48-containing TG-rich lipoproteins, called chylomicrons (CMs), which transport TGs and fat-soluble vitamins to peripheral tissues (42). Similar to its actions in the liver, insulin has a key regulatory role in the production and clearance of TRLs produced from the intestine (43). Therefore, another defining feature of diabetic dyslipidemia is elevated postprandial levels of CM particles (44). The accumulation of CM particles in insulin resistance has been attributed to decreased clearance as well as increased intestinal synthesis and secretion (45). Decreased clearance of CM and CM remnants in insulin resistance has largely been attributed to increased hepatic VLDL secretion (46), as intestinal and hepatic TRLs share common, saturable, removal mechanisms (47). Secondly, LPL activity is decreased due to diminished regulation by insulin (48), contributing to slow removal of CM and CM remnants in insulin resistance.

Although the intestine was conventionally regarded as a passive organ with respect to CM secretion, it is now evident that CM production can be actively increased in insulin resistant states (43).Insulin has been shown to directly decrease CM secretion from cultured human fetal jejunal explants (49) and to reduce CM production in healthy men following an insulin infusion (50). Mechanisms for CM overproduction in insulin resistance are unclear, yet may include increased apoB stability, increased mass and activity of microsomal triglyceride transfer protein (MTP; required for assembly of VLDLs and CMs), and enhanced DNL in the enterocyte (41,51). The inhibitory effect of insulin on CM secretion may also partly be due to its suppression of circulating FFAs (46,50,52), an effect that is blunted by insulin resistance (52) and T2D (53). Overall, human studies suggest that intestinal CM production is dysregulated in insulin resistance states, with diminished sensitivity to insulin's inhibitory effects, contributing to increased plasma CM levels. Intestinal lipoprotein production is particularly important as postprandial TG levels independently predict CVD (54). In addition, CM remnants are risk factors for atherosclerosis (55) and apoB-48 can be detected in atherosclerotic plaques (56). The intestine is also involved in the pathogenesis of MetS through its important role as an endocrine organ. The intestine secretes several gut peptides with glucagon-like peptide 1 (GLP- 1) playing a significant role in insulin secretion and signaling. GLP-1 is secreted by ileal enteroendocrine L-cells in response to a GLP-1 plays in metabolism, agonists of GLP-1, as well as inhibitors of dipeptidyl peptidase-4 (DPP-4), the main protease in GLP-1 degradation, have been successful therapeutics for T2D (58). In the pancreas, GLP-1 stimulates glucose-dependent insulin secretion, improves the capacity of β-cells to sense and respond to glucose, increases β-cell mass, and inhibits glucagon and stimulates somatostatin secretion (57).

The GLP-1 receptor (GLP-1R) and nerve fibers containing GLP-1 are located in the central nervous system and therefore several studies have examined central and peripheral actions of GLP-1. Central actions of GLP-1 include satiety promotion, reduced energy intake, and consequently decreased body weight (59). Additionally, the effects of GLP-1 on the pancreas may be mediated in part by a neural mechanism (60). In the intestine GLP-1 has inhibitory effects on lipoprotein secretion, gastric acid secretion and gastric emptying, which slows the transit of nutrients from the stomach to the small intestine, contributing to the normalization of blood glucose levels (61). The effect of GLP-1 on muscle, adipose tissue, and the liver, including stimulation of glucose uptake and inhibition of hepatic glucose production, remain controversial as to whether they are independent of changes in insulin or glucagon (57).

LABORATORY ASSESSMENT OF PEDIATRIC METABOLIC SYNDROME

An adult definition of MetS cannot simply be applied for use in the pediatric population because drastic changes in blood pressure, lipid levels, as well as body size and proportion occur with age and development. Puberty also impacts fat distribution, insulin sensitivity, and insulin secretion (62). Children develop transient physiologic insulin resistance during puberty (63), with a 25-50% decline in insulin sensitivity which recovers upon completion of pubertal development (64). The dynamic physiological changes that occur in children and adolescents has led to the lack of standardized measures in pediatrics, including measurements of central obesity (3), which is a defining feature of adult MetS. Establishing a consensus definition of MetS in the pediatric population has therefore traditionally been a challenge.

However, it is important to note that the MetS is not a disease, but a cluster of metabolic disorders. Therefore, applying any set of criteria to "define" the MetS truly reduces the complex reality of this cluster of components. Each component of the MetS is a continuous variable which gradually changes. This results in a continuum between a healthy and unhealthy metabolic profile, rather than a dichotomy of healthy and unhealthy states. However, an accepted definition of pediatric MetS is important as a diagnostic and monitoring tool to ensure standardization in clinical practice as well as in research to standardize clinical trials.

Rapid rises in obesity trends sparked the need to understand how to distinguish between children and adolescents at high risk of health complications and those with "simple" uncomplicated obesity. Traditionally, researchers have used several different definitions (65), resulting in the prevalence of metabolic syndrome varying between 0% and 60% in the same group of children, depending on the diagnostic criteria applied (66). This drove the International Diabetes Federation (IDF) to develop a universally accepted and easy to use definition for MetS in children and adolescents in 2007 (13). This definition was created with the intention to allow preventative measures to be taken before the child or adolescent develops T2D and/or CVD (13). The main component of the definition is waist circumference because it is an independent predictor of insulin resistance, lipid levels, and blood pressure (67,68). However, percentiles, rather than single cut-off points, must be used for this measure due to the dynamic metabolic changes that occur throughout the pediatric age range. A cut-off of the 90th percentile was chosen, as children and adolescents with a waist circumference $\geq$ 90th percentile are more likely to have multiple CVD risk factors (13).

The IDF consensus definition of MetS in children and adolescents is shown in Table 1. The definition excludes children who are younger than 6 years because of insufficient data for this age-group (13). For children aged 6-10 years, MetS should not be diagnosed, but those with abdominal obesity should be strongly advised to

reduce their weight. For children age 10-<16 years, MetS should be diagnosed for those with abdominal obesity and two or more other clinical features including elevated triglycerides, decreased HDL-C, increased blood pressure, and increased fasting plasma glucose. For adolescents older than 16 years of age, it is recommended to use the IDF adult criteria. This IDF pediatric definition provides a standard that facilitated comparisons of study results, including prevalence estimates across studies. However, the IDF definition of pediatric MetS is not without limitations. First, this definition does not provide criteria to diagnose children under the age of 10 years. Additionally, the blood pressure cut-off used in this definition is the same as that defined for adults and is thus too high for the pediatric population. This results in blood pressure contributing to a negligible proportion of children being classified as having the MetS using this definition (69). Lastly, rather than being based on evidence from the pediatric population, the IDF consensus definition is modified from a definition created for the adult population.

A more recent MetS definition for European pre-pubertal children was proposed by the Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects in Children and Infants (IDEFICS) Study which addresses these limitations. The main factor contributing to the absence of a consensus MetS definition in children is the lack of reference values for MetS components in the pediatric population (70).Therefore, the IDEFICS study used reference values provided by their study of European children to classify children according to the different components of the MetS (69). They propose a definition with different cut-offs to classify children requiring either close monitoring (monitoring level) or an intervention (action level) (69).

Using age-, sex-, and height- (in the case of blood pressure) specific percentiles established from the IDEFICS cohort, percentile cut-offs are defined for the Children are classified as requiring close monitoring of the MetS if three or more of these risk factors exceed the 90th percentile defined in the IDEFICS studies (69). If three or more of these risk factors exceed the 95th percentile, defined in the IDEFICS studies, an intervention is appropriate in affected children (69). They also created a simple web application (www.ideficsstudy.eu) to more easily classify an individual by entering individual measurement values and obtaining the appropriate percentiles.

As a result of using percentile cut-offs established from a pediatric population rather than arbitrary cutoffs for MetS components, the IDEFICS definition provides a more equal weight to components of the definition, allowing a more equal contribution to the overall prevalence of the MetS. However, this definition is also not without limitations. In addition to only being applicable to children and not adolescents, the percentile cut-offs for each parameter is population-specific and therefore may differ for smaller, local populations. Also, clinically relevant, prospective outcomes related to the percentile cut-offs which would allow the assessment of disease risk in relation to defining the MetS are currently lacking. In addition to proposing definitions to classify children as requiring monitoring or intervention for the MetS, the IDEFICS study also developed a quantitative CVD risk score. This was established using a z-score standardization

to calculate a continuous score combining the MetS components, with a higher score indicating a less-favorable metabolic profile. A study by Pandit et al. supports the use a quantitative risk score, as this study suggested that a continuous MetS score was a better tool to assess atherosclerotic risk in children than cut-offs of individual MetS components (71).

Table 1 **IDF consensus definition of the Metabolic Syndrome in children and adolescents**

Age (years)	Obesity (WC)	Triglycerides	HDL-C	Blood pressure	Glucose
6-<10	≥ 90th percentile	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity			
10-<16	≥ 90th percentile or adult cut-off if lower	≥1.7 mmol/L (≥150 mg/dL)	<1.03 mmol/L (<40 mg/dL)	Systolic ≥130/ diastolic ≥85 mm Hg	≥5.6 mmol/L (100 mg/dL) (If ≥5.6 mmol/L [or known T2DM] recommend an OGTT)
≥ 16 (adult criteria)	Central obesity (defined as waist circumference ≥ 94cm for Europid men and ≥ 80cm for Europid women)	≥1.7 mmol/L (≥150 mg/dL)	<1.03 mmol/L (<40 mg/dL) in males and <1.29 mmol/L (<50 mg/dL) in females, or specific treatment for these lipid measurements	Systolic ≥130/ diastolic ≥85 mm Hg, or treatment of previously diagnosed hypertension	Fasting plasma glucose ≥5.6 mmol/L (100 mg/dL), or previously diagnosed type 2 diabetes

**Table adapted from (13).*

WC: waist circumference; HDL-C: high-density lipoprotein cholesterol; T2DM: type 2 diabetes mellitus; OGTT: oral glucose tolerance test.

Rather than dichotomizing the population into children with a healthy and unhealthy metabolic profile based on cut-offs of each MetS component, the score provides a variable that accounts for gradual changes in these components. The continuous score better reflects the complex concepts of the MetS, where risk predictors lie on continuous scale and have complex interactions.

The continuous MetS score can be a useful tool in pediatric research and for evaluating interventions (69).

Table 2 IDEFICS definition of the Metabolic Syndrome in children –monitoring level

Age (years)	Obesity (WC)	Triglycerides	HDL-C	Blood pressure	Glucose
2-<11 years	≥ 90th percentile	≥ 90th percentile	≤ 10th percentile	Systolic ≥90th percentile or diastolic ≥ 90th percentile	HOMA-insulin resistance ≥ 90th percentile or fasting glucose ≥ 90th percentile

**Table adapted from (69).*

WC: waist circumference; HDL-C: high-density lipoprotein cholesterol; HOMA: homeostatic model assessment.

In addition to the parameters included in the consensus definitions of pediatric metabolic syndrome, the standard lipid profile aids in CVD risk assessment. A standard lipid profile includes fasting measurements of plasma or serum concentrations of total cholesterol, LDL-C, HDL-C, and triglycerides. Additional markers that have been added to the lipid profile in some clinical laboratories include non-HDL cholesterol, apolipoprotein B (apoB), apolipoprotein A1 (apoA1), and lipoprotein(a) (Lp(a)) (72). Non-HDL cholesterol, calculated as total cholesterol minus HDL-C, gives an indicator of the total cholesterol content of atherogenic lipoproteins. ApoB and apoA1 can also be used as alternatives to non- HDL and HDL cholesterol, respectively, where they indicate the particle number, rather than cholesterol content. Lastly, Lp(a) should only be determined in the same patient once as its concentration varies little over time.

POTENTIAL NOVEL BIOMARKERS IN LABORATORY ASSESSMENT OF PEDIATRIC METABOLIC SYNDROME

With the increasing public health burden of MetS, the identification and examination of novel biomarkers able to detect MetS and subsequently CVD risk early, with high specificity and sensitivity, is a clinical priority (73). Effective MetS biomarkers maximize the effectiveness of treatment in subjects who would benefit the most. The association of MetS with several systemic alterations that involve numerous organs and tissues adds to the complexity and challenge of identifying MetS biomarkers. A few categories of potential MetS biomarkers and nontraditional pre-analytical considerations that have recently been gaining interest will be discussed.

ADIPOCYTOKINES

Recent literature has shifted the notion of adipose tissue as a nonfunctional energy storage site to an important secretory organ.

Adipose tissue secretes low-molecular weight peptides, called adipocytokines, which have numerous functions including food intake regulation, glucose and lipid metabolism, and inflammation (74).

More recently, studies have shown adipocytokines mediate obesity-associated metabolic disorders independently of other risk factors (75). One adipocytokine, adiponectin, is secreted primarily by the adipocyte and is actually decreased in plasma upon an increase in fat mass (76).Adiponectin has several functions including anti-inflammatory and anti-atherogenic effects, as well as insulin sensitization and lipid regulation (77). Pediatric studies have shown that plasma adiponectin concentration is inversely correlated with BMI, waist circumference (WC), fasting insulin concentration, and insulin resistance (78,79) and is 25% higher in healthy overweight youth compared to those with MetS (80). Additionally, a study of 5,088 adolescents showed that a decreased adiponectin concentration was associated with an increased risk of MetS, independent of age, BMI, WC, and total cholesterol (81).

Leptin, the first identified adipocytokine, is a product of the obesity gene and is known as the "satiety hormone" because it decreases food intake and increases energy expenditure. Leptin concentration has been shown to reflect body fat mass and, as a result, can be considered a reliable marker of fat mass and energy homeostasis in non-insulin resistant individuals (82). Not only do obese individuals tend to have elevated plasma leptin concentrations, but they are also leptin-resistant, negating the beneficial effects of leptin (83).

Several studies have also shown this positive association between fat mass and leptin concentration in the pediatric population (84,85). Furthermore, leptin is positively associated with insulin resistance in pre-pubertal children after adjusting for sex, age, and BMI, and for every 1 ng/dL increase in leptin levels, the odds of MetS increase by 3%, suggesting an important role for leptin as a marker of CVD risk (86).

As a result of several studies supporting the potential roles of both adiponectin and leptin as MetS biomarkers, studies to develop normative values for adiponectin were warranted. A study in 2012 established sex-specific reference intervals (2.5th and 97.5th percentiles of concentration distribution in healthy subjects) for total adiponectin in cord blood and for each one year interval from 0-14 years of age (87). Another study of 111 healthy children aged 0-10 years provided median, 25th and 75th percentile values for leptin (88).

A more recent study established age- and sex-specific reference intervals for both serum adiponectin and leptin in pre-pubertal European children (ages 3-9 years) (89). Furthermore, studies have assessed the diagnostic potential of these biomarkers in the pediatric population. One study determined an adiponectin concentration of 6.65 μg/mL as a cutoff point to identify MetS with 64% and 67% sensitivity and specificity, respectively (75). Likewise, a recent study determined a leptin level of 13.4 ng/mL as a cutoff point to identify MetS with a sensitivity and specificity of 68% and 69%, respectively (86).

Although further examination of these biomarkers is needed to determine their suitability in MetS detection, extensive progress has been made in the understanding of these adipocytokines in pediatric MetS.

MICROALBUMIN

Microalbuminuria, an increased level of urine albumin, is thought to be the renal expression of vascular endothelial damage, particularly increased vascular permeability, as evidence suggests that glomerular leaking of albumin reflects general vascular damage (90–92).

Therefore, microalbuminuria denotes preclinical atherosclerosis and can be used as an early atherosclerosis indicator (90–92). Obesity is strongly associated with the two most common causes of end-stage renal disease: diabetes and hypertension (93). Additionally, the MetS is suggested to be an independent risk factor for both chronic kidney disease and end-stage renal disease (94). Initially introduced into the criteria to define the MetS by the WHO in 1988 (14), microalbuminuria screening is now recommended to be added to the assessment of the CVD risk profile in adults (92). This is the result of well-established evidence of the relation between microalbuminuria and hypertension, central adiposity, the MetS, and CVD mortality (95). More recent studies have examined the association between microalbuminuria and obesity as well as other CVD risk factors in the pediatric population (93,96,97). A study of 150 obese children by Sanad M et al. found that obese children with microalbuminuria had a significantly higher blood pressure, triglyceride levels, LDL levels, as well as a higher prevalence of MetS, insulin resistance, and impaired fasting glucose levels, than those without microalbuminuria (93). Another study by Burgert T et al. found that 10.1% of an obese, non-diabetic pediatric cohort had a urine albumin to creatinine ratio in the microalbuminuric range (i.e. 2-20 mg/mmol), which is similar to the expected prevalence in an obese adult population (96). Even slight abnormalities in glucose metabolism may promote early vascular damage in pediatric obesity (96). Microalbuminuria has been suggested as a treatment target in adults (98,99), and now may also become an approachable treatment target in pediatric metabolic syndrome, potentially responsive to treatment (i.e. lifestyle intervention or pharmacotherapy) directed at improving insulin sensitivity and glucose tolerance (96).

GUT PEPTIDES

In contrast to the extensively studied adipocytokines, gut peptides, including GLP-1 and GLP- 2, are more novel potential biomarkers that are gaining interest in parallel with the recently accepted metabolic role of the intestine. In addition to its well-known incretin action, GLP-1 also promotes satiety, inhibits gastric emptying, and regulates lipid metabolism (57). Studies have shown decreased GLP-1 secretion and blunted postprandial increase in GLP-1 in morbidly obese (83) and T2D individuals (100). This may be due to the decreased responsiveness of L-cells to nutrient intake in insulin resistant conditions (101).

With the important incretin effect of GLP-1, it is evident that decreased GLP-1 secretion in an obese state would have implications on insulin action.

Recent pediatric studies have shown that fasting total GLP-1 is reduced, but fasting active GLP-1 is elevated in obese compared to normal weight adolescent girls (102). Overall, GLP-1 secretion and plasma concentration in obesity remains controversial and pediatric studies of this phenomenon are extremely limited. GLP-2, encoded on the same gene and co-secreted in an equimolar amount with GLP-1, enhances intestinal lipoprotein production and nutrient absorption, as well as reduces inflammation (86). Recent studies in obese adults have shown an inverse relationship between GLP-2 secretion and insulin sensitivity, although the underlying mechanisms are still unknown (103). Studies on GLP-2 are even more scarce, particularly on obese pediatric subjects. Future studies examining the potential of GLP-1 and GLP-2 as MetS biomarkers in pediatric subjects are critical to understand their potential in laboratory assessment of pediatric MetS.

LIPOPROTEINS AND APOLIPOPROTEINS

Although the standard lipid profile consists of lipids and lipoproteins, with some newly added apolipoproteins, there are additional lipoprotein subfractions recently receiving attention for CVD risk assessment. The first parameter, remnant lipoproteins (RLPs) are metabolic products of TG-rich lipoproteins (i.e. CMs and VLDLs). A study of 1,567 women from the Framingham Heart Study showed RLP-C was an independent risk factor for CVD in women, independent of TG (55). Postprandial RLP-C was shown to be an independent predictor of insulin resistance after adjusting for age, BMI, and other lipid profiles in a study of 78 adults (104).

Pediatric studies have shown that RLP-C is significantly higher in obese subjects and strongly related to insulin resistance (91). Long-term prospective studies are needed to evaluate whether children and adolescents with high RLP-C are at greater risk of developing MetS. The second parameter is apoB-48 which is a specific marker of intestinal lipoproteins (i.e. CMs). As CMs are secreted in the postprandial state, apoB-48 can subsequently be used to examine postprandial lipoprotein metabolism (91). Adult studies have shown fasting apoB-48 is elevated in subjects with MetS (105) and T2D and is significantly associated with endothelial dysfunction (106).Recent studies in pediatrics determined that fasting plasma apoB- 48 can subsequently be used to examine postprandial lipoprotein metabolism (91). Adult studies have shown fasting apoB-48 is elevated in subjects with MetS (105) and T2D and is significantly associated with endothelial dysfunction (106). Recent studies in pediatrics determined that fasting plasma apoB-48 concentration is 2-fold higher in obese versus normal weight subjects (107). However, pediatric data on apoB-48, particularly in the postprandial state, is needed to understand the potential of apoB-48 as a MetS biomarker.

ASSESSMENT IN THE POSTPRANDIAL STATE

In addition to the recent exploration of novel MetS biomarkers, emerging pre-analytical conditions that may improve both the simplicity of laboratory testing and the relevance of the laboratory test results have been examined. In clinical practice, the lipid profile is traditionally measured in a fasting state even though the postprandial state predominates over a typical 24 hour day.

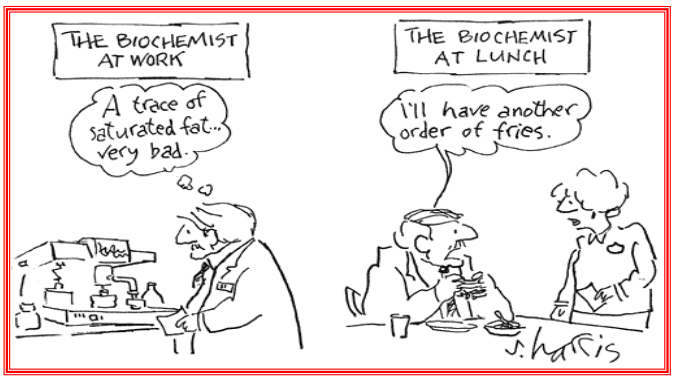
Therefore, the lipid and lipoprotein content of a fasting sample does not accurately reflect the daily average concentration of these parameters. Additionally, evidence is lacking that a fasting sample is superior to a postprandial sample when evaluating for CVD risk assessment, and in fact, postprandial samples seem to be more advantageous (72). Some advantages include simplification of blood sampling for patients, particularly pediatrics, improving patient compliance with lipid testing, and decreasing the volume burden on laboratories in the morning. Several studies have found that postprandial lipid and lipoprotein measurements suffice for CVD risk screening, and in some cases are even better predictors (72). As MetS is a cluster of CVD risk factors, postprandial measurements may be more relevant for clinical guidelines. For example, a meta-analysis including over 300,000 individuals found that postprandial non-HDL cholesterol and calculated LDL-C were superior to fasting measurements for predicting CVD risk (108). Furthermore, the novel MetS biomarkers discussed here are more relevant following nutrient ingestion.

For example, GLP-1 and GLP-2 concentrations are much more relevant in the postprandial state, as their concentrations in the fasting state are very low and their secretion is stimulated upon nutrient ingestion (95). Additionally, approximately 80% of the postprandial increase of TG is due to the increase in TG of RLPs (109) and apoB-48 is a marker of CMs (i.e. lipoproteins secreted from the intestine following a meal).

Therefore, if MetS components lead to an alteration in these biomarkers, this change would be apparent in the postprandial, rather than fasting state.

CONCLUDING REMARKS

The clustering of CVD risk factors, termed the metabolic syndrome, is present in both adults and children. MetS is primarily driven by excess adipose tissue and subsequent insulin resistance. Insulin resistance manifests in several organs, including the muscle, liver, and intestine, and as a result is associated with several systemic complications including hypertension, dyslipidemia, and impaired glucose tolerance. The interplay of metabolic dysfunction in several organ systems leads to the development of atherosclerosis and consequent CVD complications. Defining MetS in the pediatric population has been controversial due to the difficulties of generalizing both a diverse syndrome and a diverse population. However, establishing a consensus definition is critical for identification and management of youth at a higher risk of developing CVD. As a result, the examination of novel MetS biomarkers in the pediatric population has been of interest to identify pediatric subjects with obesity-related metabolic complications early before CVD complications manifest.



FORTHCOMING EVENTS:

ACBI Election Notice

Call for Nominations to fill up vacancies in

Executive Council of ACBI – 2019.

Position		Number of Vacancies
1. Vice President	:	One
2. State Representatives	:	All the States

Duly filled nominations for the above posts are invited from the eligible members duly proposed and seconded by the Members of the Association. Nominations may please be submitted to the President, ACBI in the format given below to either by post or to his email : profaamahdi@gmail.com

Dr. Abbas A. Mahdi
Vice-Chancellor
Era University
Sarfarazganj, Hardoi Road
Lucknow - 226003
UP

The Last date for receiving the Nominations: October 10th, 2018

The Last date for withdrawal of Nominations: November 15th, 2018

Dr. Rajiv R. Sinha
General Secretary, ACBI

Note: Required Qualifications for various posts:

Vice President-II: A candidate for this posts should be a life member of at least 10 years standing and have attended at least 7 Annual Conferences of the Association. He/ She should be holding a senior post in his/her work place or has been doing clinical biochemistry for the last 15 years. Candidates should not hold any bias against medical-non-medical members or bias against any one.

He / she have shown aptitude for working for the association by taking up some responsibilities of the Association in the past.

State Representative should be a life member who has attended conferences regularly in the last 5 years and is fairly active in Association activities.

FORMAT OF THE NOMINATION FORM FOR POSITIONS IN EXECUTIVE COUNCIL

I, …….…….. propose the name of Prof. / Dr. / Mr./ Ms. ..... bearing ACBI Membership No..... for the post of .....

Place : **Signature:**

Date: **Membership number :**

I, ……. second the proposal

Place : **Signature:**

Date: **Membership number :**

I …….. accord my consent to the proposal

Place : **Signature:**

Date: **Membership number :**

[Please attach photocopy of ACBI Member ID card & required number of Conference Attendance certificate along with application t support your nomination.]

An Infant with Persistent Jaundice and a Normal Newborn Direct Bilirubin Measurement

Sanjiv Harpavat, Sridevi Devaraj, *Milton J. Finegold*

DOI: 10.1373/clinchem.2014.223115 Published January 2015

CASE DESCRIPTION

A 54-day-old infant of Asian descent presented with jaundice. He first started appearing yellow a few weeks after birth. His pediatrician initially recommended increasing sunlight exposure. At subsequent visits, the pediatrician recommended stopping breastfeeding. Despite these interventions, the infant's jaundice persisted and his stools became pale. At 52 days of life (DoL),3he had a serum bilirubin measured, and the reported "Bilirubin, Direct" concentration of 5.54 mg/dL (reference interval, 0.0–0.4 mg/dL) prompted an immediate referral (see Table 1 for a summary of laboratory results).

Table 1. Summary of fractionated bilirub in results.

Day of life	Test name	Assay	Instrument	Result, mg/dL	Reference interval, mg/dL	Reference interval source
1	"Neonatal Dbil"	Direct spectrophotometry	Vitros	0.5	0.0–0.6	Manufacturer
52	"Bilirubin, Direct"	Chemical reaction (Diazo)	Roche	5.54	0.0–0.4	Laboratory derived
54	"Bili Conjugated"	Direct spectrophotometry	Vitros	4.7	0.0–0.2	Laboratory derived

The infant's physical examination and evaluation results were most consistent with biliary atresia (BA). He had marked jaundice, with a reported "Bili Conjugated" of 4.7 mg/dL (reference interval, 0.0–0.2 mg/dL), as well as increased aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase activities. He otherwise appeared well and had 2 newborn screens with results within reference intervals, making infectious or metabolic etiologies unlikely. Furthermore, protease inhibitor typing, chest radiograph, and abdominal ultrasound revealed no abnormalities, arguing against other liver-associated causes such as α_1-antitrypsin disease, Alagille syndrome, and choledochal cyst.

There was one laboratory result, however, that was inconsistent with BA: his newborn conjugated bilirubin concentration, reported as "Neonatal Dbil."

In our experience, infants with BA have newborn direct or conjugated bilirubin concentrations that exceed their birth hospital's derived reference interval (1).

In contrast, this infant had a reported "Neonatal Dbil" concentration of 0.5 mg/dL on DoL 1, which was within the birth hospital's reported reference interval of 0.0–0.6 mg/dL. The bilirubin was measured using a Vitros analyzer, and the reference interval was derived by the manufacturer based on "40 apparently healthy neonates" (2).

QUESTIONS TO CONSIDER

- What is the difference between "Neonatal Dbil," "Bilirubin, Direct," and "Bili Conjugated"?
- How should reference intervals be established?
- Why are the reference intervals for the 3 tests in **Table 1** different?

Because infants with BA treated earlier have the best outcomes, we continued the evaluation despite the discrepant newborn bilirubin concentrations. He promptly underwent liver biopsy, which showed fibrosis and bile duct proliferation characteristic of BA. Subsequent intraoperative cholangiogram confirmed the BA diagnosis. However, one important question still remained: how could the infant's reportedly normal "Neonatal Dbil" concentration at birth be explained?

DISCUSSION

As many as 15% of infants may present to their pediatricians for evaluation of jaundice (3). Most have increased unconjugated bilirubin concentrations, which can usually be treated supportively with increasing sunlight exposure or switching from breast milk to formula. Some infants, on the other hand, have high conjugated bilirubin concentrations. These infants may have more serious diseases that require prompt intervention, because increased conjugated bilirubin concentrations are a marker for a variety of infectious, metabolic, and/or liver conditions.

For infants with increased conjugated bilirubin concentrations, practitioners should review the bilirubin measurements in the newborn period to help make the diagnosis. Newborn total bilirubin concentrations are often measured to determine need for phototherapy and, as in this case, total as well as conjugated (commonly referred to as "Dbil," "direct," or "conjugated") Concentrations are reported.

If the newborn conjugated concentration is high, the practitioner can assume the infant was born with disease and should suspect metabolic or liver-related causes. If the newborn conjugated concentration is within reference intervals, the practitioner can assume the infant acquired the disease sometime after birth and should consider infectious causes more likely. Unfortunately, as highlighted by this case, practitioners face a number of challenges in interpreting newborn conjugated bilirubin concentrations correctly. Our infant did indeed have high conjugated bilirubin concentrations at birth, consistent with his diagnosis of BA. However, his newborn concentration was overlooked because of 2 subtle yet critical details: (*a*) the result was reported as "Dbil," when in fact "conjugated" bilirubin was assayed; and (*b*) the reference interval was too broad for newborn "conjugated" bilirubin assays. How these errors occurred-and continue to occur—can be understood by examining the nuances of conjugated bilirubin measurements.

CONJUGATED BILIRUBIN IS INCREASED IN LIVER DISEASE

Serum generally contains 2 types of bilirubin. The first type, unconjugated bilirubin, forms when old red blood cells are cleared and heme is degraded. Unconjugated bilirubin can present a problem in neonates, because increased concentrations can accumulate in the developing brain and cause the devastating neurological disease kernicterus. As a result, high unconjugated concentrations in newborns are treated with phototherapy, which lowers unconjugated bilirubin by converting it to dozens of different isomers that are more efficiently cleared from the circulation (4).

The second type, conjugated bilirubin, is formed when hepatocytes process unconjugated bilirubin for excretion. Hepatocytes collect unconjugated bilirubin from the circulation and make it more water soluble by attaching—or conjugating—1 or 2 glucuronide moieties to bilirubin through a well-characterized esterification reaction. Hepatocytes then secrete the bilirubin mono- and diglucuronide into the canalicular space, where it dissolves in bile and ultimately passes out of the body with stools **(4).**

Conjugated isoforms accumulate in serum in a variety of liver diseases. For example, bilirubin mono- and diglucuronide concentrations can increase if hepatocytes lyse (as in viral infections) or if bilirubin is not transported across the hepatocyte's membrane correctly (as in Dubin-Johnson syndrome). They can also increase in diseases such as BA where bile ducts are obstructed. Normal bile flow ceases, preventing all components of bile, including conjugated bilirubin, from passing appropriately. Instead, bile backs up into the liver and eventually into the bloodstream.

Delta bilirubin is a third form of conjugated bilirubin, which is only present in chronic liver diseases. Delta bilirubin forms when serum concentrations of bilirubin mono- and diglucuronide are so high that some covalently bind with albumin. Delta bilirubin's bond with albumin is essentially irreversible, and delta bilirubin clearance follows the slow kinetics of albumin clearance. As a result, delta bilirubin concentrations can be present even after bilirubin mono- and diglucuronide have been cleared and a patient's primary liver problem has resolved **(4).**

DIRECT AND CONJUGATED ASSAYS ARE NOT EQUIVALENT

The first issue in this case was an issue in reporting. The laboratory reported a "Dbil" result when in fact "conjugated" bilirubin was assayed. "Direct" and "conjugated" bilirubin assays are widely available, and, as in this patient, are often performed in the same patient at different times. As a result, the 2 are often confused and used interchangeably. However, the 2 are very different assays, measuring different bilirubin fractions using unrelated technologies.

"Direct" bilirubin assays measure all conjugated bilirubin (bilirubin monoglucuronide, bilirubin diglucuronide, and delta bilirubin) as well as some unconjugated bilirubin. "Direct" assays involve a chemical reaction with diazo dyes, followed by quantification of azobilirubin produced over a specified time. All conjugated bilirubin forms react quickly, whereas unconjugated bilirubin forms react more slowly (unconjugated bilirubin forms can react quickly if an accelerant is added, as is done for total bilirubin measurements). Hence, the "direct" assays always include delta bilirubin and a small amount of unconjugated bilirubin **(4).**The "conjugated" bilirubin assay, on the other hand, measures bilirubin mono- and diglucuronide alone. This assay is based on direct spectrophotometry, using the BuBc slide on the Vitros analyzer.The BuBc slide shifts the absorbance spectrum of bilirubin mono-/diglucuronide by 30–40 nm, thereby allowing these forms to be quantified separately from unconjugated and delta forms (5). As a result, "conjugated" measurements are usually less than "direct" measurements, because they do not include delta bilirubin or any unconjugated bilirubin [compare DoL 54 and 52 concentrations in this case **(Table 1)].**

Though "direct" and "conjugated" assays are the most commonly available, they are not the only ways to measure conjugated bilirubin concentrations. For example, the bilirubin oxidase and vanadate oxidation methods are enzymatic and chemical assays, respectively. They involve converting conjugated bilirubin forms into biliverdin and, unlike the diazo method, are unaffected by coexisting substances such as hemoglobin or vitamin C **(6).** HPLC, currently used mainly for research purposes **(4),** can also be used. HPLC offers the advantage of detecting minor bilirubin fractions such as those produced with phototherapy.

"DIRECT" AND "CONJUGATED" REFERENCE INTERVALS SHOULD BE VERIFIED

The second issue in this case was an issue of borrowing reference intervals. Many laboratories face challenges with pediatric reference intervals. Few have the resources to derive their own ranges of values for every test and age. Instead they borrow reference intervals from manufacturers, and now, more recently, from large initiatives such as the CALIPER (Canadian Laboratory Initiative on Pediatric Reference Intervals) database **(7).** In many scenarios, this is appropriate; however, "direct" and "conjugated" bilirubin assays deserve special consideration.

For example, "direct" assay methods differ from laboratory to laboratory, complicating the use of a single reference interval. "Direct" measurements using the diazo method vary depending on a number of site-specific factors, including how long the chemical reaction is allowed to proceed, the pH of the reaction, the strength of the diazo reagents, and the instrument used (4). As result, reference intervals that combine data from many laboratories, such as a published range of approximately 0.0–1.0 mg/dL from 2898 infants age 0–14 days, are too broad to be of practical use (8). Instead, derived reference intervals similar to the range from the DoL 52 measurement in this case are clinically more meaningful.

For the "conjugated" assay, borrowing reference intervals poses a different problem, as demonstrated in this case. The "conjugated" assay should vary less from laboratory to laboratory because it always uses the same reagent (the BuBc slide) and is performed on the same instrument (the Vitros analyzer). However, the manufacturer's reference interval of 0.0–0.6 mg/dL does not match that derived in clinical practice. For example, a much narrower range of 0.0–0.3 mg/dL was calculated from 64095 newborns ages 0–14 days who had a clinical reason to have bilirubin measured (8). Similarly, our hospital and others with the Vitros analyzer independently derived a reference interval of 0.0–0.2 mg/dL by using concentrations from cohorts of healthy newborns.

We surmise 2 reasons for why such a broad reference interval was used by the manufacturer. First, the manufacturer may have used too small of a sample size for their reference interval calculations. The manufacturer reports using measurements from 40 newborns for its reference interval, whereas the standard is to calculate reference ranges using samples from at least 120 individuals (2, 9). Second, widening the reference interval could reduce false positives and increase specificity. The upper limit of the reference interval is traditionally defined as the highest 2.5% of concentrations, resulting in increased concentrations in as many as 1 in 40 cases. By broadening the reference interval beyond the standard limits, the high positive rate would certainly decrease; however, it does so at the expense of missing cases with serious disease, such as the infant in this case.

CLINICAL IMPLICATIONS

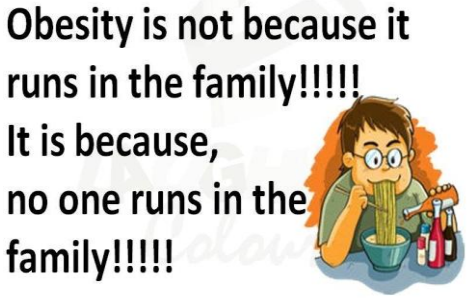
The newborn in this case was overlooked because of 2 subtle but clinically important problems, which we were able to uncover only after considerable investigation. The most important clue was realizing that the laboratory was actually measuring "conjugated" bilirubin concentrations. Whereas a "direct" bilirubin concentration of 0.5 mg/dL could be within the reference interval because of

measurement variations, a "conjugated" bilirubin concentration of 0.5 mg/dL is well above all published and independently derived reference intervals. This discrepancy prompted us to further question how the laboratory obtained its reference intervals.

Importantly, if only 1 of the 2 problems had occurred, this infant could have been recognized in the newborn period. For example, had the test been labeled correctly, some providers would have recognized the high "conjugated" bilirubin concentration despite the reference interval provided. Similarly, had a narrower reference interval been used, all providers would have identified the bilirubin concentration as abnormal regardless of how the test was labeled. Unfortunately, when both problems are combined, the test result becomes impossible to interpret correctly without more information. Theoretically, the error prevented what could have been an earlier diagnosis and treatment, which in turn correlates with delaying or even preventing need for liver transplantation (10). With an abnormal newborn concentration, the infant's pediatrician would have been advised to repeat the test at the 2-week well-child visit. Although this method introduces a small delay, in our experience it effectively excludes many of the newborns who test high but do not have liver disease. This infant would have retested high at 2 weeks and would have then been referred to us urgently. We would have performed an identical evaluation, but treatment would have been given before the DoL 30 mark instead of after DoL 54. Hence, while not diagnostic for BA, newborn conjugated bilirubin concentrations—if reported correctly with appropriate reference intervals—have the potential to accelerate the BA diagnosis and ultimately improve how infants fare with the disease.

POINTS TO REMEMBER

- Newborn "direct" and "conjugated" bilirubin concentrations can help identify infants with serious liver diseases such as BA.
- "Direct" assays use a chemical reaction and measure bilirubin monoglucuronide, bilirubin diglucuronide, delta bilirubin, and a small amount of unconjugaed bilirubin.
- The "conjugated" assay uses spectrophotometry and measures bilirubin monoglucuronide and bilirubin diglucuronide.
- Reference intervals for newborn "direct" or "conjugated" bilirubin concentrations should be verified independently by each laboratory.



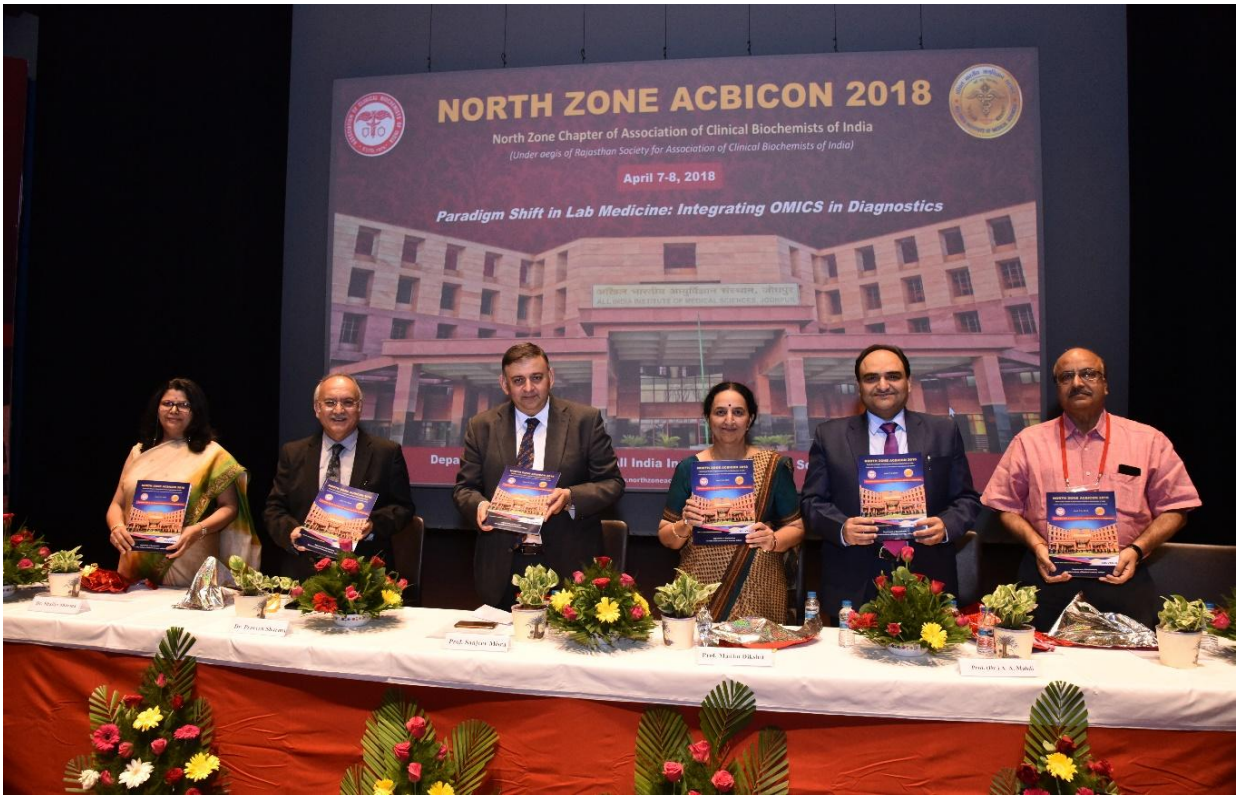
NEWS FROM BRANCHES/ZONES

NORTH ZONE CONFERENCE OF ACBI

North Zone ACBICON 2018 based on apt theme "Paradigm shift in Lab medicine: Integrating omics with diagnostics" was held in AIIMS Jodhpur on 7th& 8th April 2018. The conference was organized by the Department of Biochemistry, All India Institute of Medical Sciences, Jodhpur under aegis of Rajasthan Society for Association of Clinical Biochemists India. The two days conference was inaugurated by Prof Madhu Dikshit, Former Director CSIR, and Lucknow. Prof Abbas Ali Mahdi President ACBI, Prof Rajeev R Sinha General Secretary ACBI, Prof Sanjeev Mishra, Director AIIMS Jodhpur and Prof Praveen Sharma were the eminent personalities present on the dais. Inauguration began with the lighting of the lamp by the honorable guests. Welcome note was delivered by the patron Prof Praveen Sharma.

The luminaries on the dais unveiled the souvenir which was followed by keynote address by Prof Madhu Dixishit. The vote of thanks was delivered by Dr Shailja Sharma, the state representative ACBI.

This conference observed participation from experts from various fields at a platform where delegates were enlightened by the experts about the rapidly emerging area of OMICS integration in lab diagnostics. The two days wholesome scientific sessions comprised eight symposia targeting the various important areas targeting newer biomarkers and research related to patient health. The conference observed participation of 150 delegates. To encourage research in youngsters two best oral presentations were awarded cash prize of Rs 1000 and Rs. 500 and six poster entries were given cash prize of Rs 500 each in the valedictory function.



WEST ZONE CONFERENCE OF ACBI

The ACBI west Zone One Day Lecture Series was conducted in Tata Memorial hospital, on Sunday, 8th July 2018. This event was graced by over 160 delegates from different parts of the country. The day was started with the lamp lighting ceremony, by all the dignitaries on the dias, including Dr. Sucheta Dandekar, Chief Guest and past president of ACBI & Dr. Rohini Bhadre, ACBI representative for Maharashtra. After a few welcoming words by Dr. Sangeeta Desai, Head dept. of Pathology, TMH, the programme was inaugurated by Dr. Dandekar. She spoke about the importance of quality and quick results in the management of ailments such as cancer. This was followed by a very enthralling scientific session with speakers from various backgrounds, namely Dr. Rajiv Sarin (Rad. Oncologist), Dr. Geeta Rathnakumar (Biochemist), Dr. Kanjaksha Ghosh (Hematologist), Dr. Nitin Inamdar (Biochemist), Dr. Shruti Kate (Oncologist), Dr. Barnali Das (Biochemist), Dr. Anuradha Choughule (Mol. Bio), Dr. Milind Bhide (Pathologist) & Dr. Kinjalka Ghosh (Biochemist). The speakers highlighted the importance of biochemistry in cancer biology and recent trends in cancer biochemistry. It also included a Panel discussion about "Problems arising in various kinds of labs". The panelists for this discussion were Dr. Sucheta Dandekar representing Govt. Labs, Dr. Alap Christy representing a Private Chain of Diagnostic centres, Dr. Barnali Das from a corporate Hospital & Dr. Suchit Naiksatam from a standalone lab's perspective. All the panelists highlighted various problems faced by their respective labs and offered how they may approach to solve them. It was a very healthy discussion.

The CME was finally concluded by felicitating all the speakers, panelists, winners of Quiz and Poster competitions and the Vote of thanks.

Dignitaries (L-R): *Dr. Rohini Bhadre, Dr. Rajiv Sarin, Dr. Sucheta Dandekar (Chief Guest), Dr. Sangeeta Desai, Dr. Bharat Rekhi, Dr. Nitin Inamdar (OIC-Biochemistry TMH).*

Poster Competition

Department of Biochemistry, Tata Memorial Hospital, Mumbai.

Organizing Secretaries: Dr. Kinjalka Ghosh & Dr. Geeta Rathnakumar

WEST ZONE CONFERENCE OF ACBI

The National Conference "Central Zone ACBICON" 2018 was jointly organized by Department of Biochemistry, King George's Medical University, Lucknow and Era University at Era University, Lucknow on 21st & 22nd July 2018. Conference was aimed to "translate" a better platform for clinicians, researchers and educators to present and discuss the most recent innovations, trends, as well as practical challenges encountered and solutions adopted in the fields of Molecular Medicine. An exciting and informative scientific program was prepared by the scientific committee in which excellent interactive educative sessions by world renowned experts were conducted. More than 25 learned experts shared their experiences and talked about the latest research and developments in the field of Medical Biochemistry. The conference was attended by more than 200 delegates. Participants experienced a breath of learning and continuing education opportunities, as was rightly depicted in the theme of the conference, "Recent Advancements in Molecular Diagnostics". The registration and welcome for the conference commenced at 8:30 am on 21st July 2018. Session I of the conference started with the invited talk by Dr. Saheem Ahmad from Integral University, Lucknow on the topic "Anti-diabetic and Anti-glycation activity of Ellagic acid in Experimental Diabetic Animals". He explored the anti-glycation activity of Ellagic acid in diabetic rats. This was followed by an invited lecture from Dr. Neetu Nigam, KGMU, Lucknow on "Recent Advancements in Diagnosis of Chromosomal Abnormalities". She highlighted the advances in cytogenetic tools like Fluorescence in situ hybridization (FISH), a procedure to find the positions of specific DNA sequences on chromosomes, which play a crucial role in accurate and early identification of chromosomal abnormalities and also help in possible treatment and management. Dr. Sukhes Mukherjee, from AIIMS, Bhopal spoke on the topic "Biochemical and Haematological Investigations associated with Pulmonary Tuberculosis Patients". He explained the homeostasis between the inflammatory cytokines and protective immune response. Dr. Sudhir Mehrotra, from Lucknow University, Lucknow & Dr. Wahid Ali from KGMU, Lucknow were the Chairperson of this session.After the tea break, scientific session II started with Chairpersons Dr. Arun Raizada from Medanta-The

Medicity, Gurgaon & Dr. Alpana Sharma from AIIMS, New Delhi. Session started by invited talk of Dr. S. P. Verma from KGMU, Lucknow on "Impact of molecular diagnosis on management of haematological malignancies". He defined the management of different haematological malignancies. Dr. Ruchi Gupta, from SGPGI, Lucknow spoke on "Molecular basis of classification of hematological malignancies". She explored ultimate aim of refining the molecular diagnosis of the hematologic cancers in the development of new potential targeted therapy. Other invited talk by Dr. Tasleem Raza, from Era University, Lucknow on "Recent advances in the Molecular Diagnosis of Hematological Malignancies: Next Generation Sequencing (NGS)". He spoke on Molecular diagnostics which included PCR, RT PCR, microarrays, DNA sequencing (Sanger & NGS) etc. Next generation sequencing technologies have evolved to revolutionize an accurate and comprehensive means for detection of genetic mutations in haematological malignancies with a cost effective manner.Dr. Khaliqur Rahman from SGPGI, Lucknow spoke on "Role of Flow Cytometry and Fluorescent In Situ Hybridization in Acute Leukemia". He highlighted about acute leukemia with a range of clinical presentations and different treatment protocols. Additionally, they provided the information required for the genetic risk stratification for further guiding the treatment. Last lecture of this session was delivered by Dr. Sudhir Verma, a application scientist of Thermofisher on the topic "Clinical Application on NGS & CE platform". He described Sanger sequencing and wide range of DNA sequencing applications: such as De novo sequencing, Targeted DNA sequencing, Next-generation sequencing validation, HLA sequencing, Mitochondrial sequencing etc.After the tea break, scientific session II started with Chairpersons Dr. Arun Raizada from Medanta-The Medicity, Gurgaon & Dr. Alpana Sharma from AIIMS, New Delhi. Session started by invited talk of Dr. S. P. Verma from KGMU, Lucknow on "Impact of molecular diagnosis on management of haematological malignancies". He defined the management of different haematological malignancies. Dr. Ruchi Gupta, from SGPGI, Lucknow spoke on "Molecular basis of classification of hematological malignancies". She explored ultimate aim of refining the molecular diagnosis of the hematologic cancers in the development of new potential targeted therapy. Other invited talk by Dr. Tasleem Raza, from Era University, Lucknow on "Recent advances in the Molecular Diagnosis of Hematological Malignancies: Next Generation Sequencing (NGS)". He spoke on Molecular diagnostics which included PCR, RT PCR, microarrays, DNA sequencing (Sanger & NGS) etc. Next generation sequencing technologies have evolved to revolutionize an accurate and comprehensive means for detection of genetic mutations in haematological malignancies with a cost effective manner.

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The Conference was inaugurated by the chief guest of the occasion Prof. Dr. Raj Kumar, Hon'ble Vice Chancellor, of UP University of Medical Sciences Saifai, Etawah, U.P, Lucknow. Prof. M. L. B. Bhatt, Hon'ble Vice Chancellor of King George's Medical University, Lucknow was the Guest of Honor of the occasion.

The inaugural function was presided over by Prof. Abbas Ali Mahdi, Hon'ble Vice Chancellor of Era University. He welcomed the delegates and guests and said that it is a matter of great pride that for the first time ACBI conference is being organized at Era University, Lucknow. He said that the organizing committee has made concerted efforts to organize events for the benefit of the participants. He said that these types of conferences are important for the continuous update of knowledge. Welcome address was delivered by Dr. Shivani Pandey, Organizing Secretary of the conference. She welcomed the delegates and guests and said that I am sure that the conference will provide an excellent platform to the younger generation to learn about latest developments in the field of Medical Biochemistry from the leading experts of the fields.

Addressing the participants Chief Guest Prof. Dr. Raj Kumar congratulated the organizing committee for organizing such a great scientific extravaganza. He said that these types of events are very important for continued update of knowledge.

He said that participants must utilize this opportunity to learn and update their knowledge. He complimented the Department of Biochemistry, King George's Medical University, and Era University for organizing the conference for the benefit of young faculty, residents and research scholars. Guest of Honor Prof. M. L.B Bhatt congratulated the organizing team of the conference for organizing such a well organized conference. He appreciated the research work undertaken by the Department of Biochemistry where more than 40 research papers are being published annually which is a big achievement. He further stated that this is the only department which is having the National Referral Centre for Lead Poisoning in addition to Molecular Cell Biology, Cell Culture, Free Radical Research & Metal Toxicity, and Natural Product Research Laboratory under one roof. At the end of the function, Dr. Dilutpal Sharma, Head, Department of Biochemistry, King George's Medical University, Lucknow proposed vote of thanks. He thanked the distinguished guests and delegates.

The programme was conducted by Dr. Kalpana Singh, Associate professor Department of Biochemistry, KGMU, Lucknow. The function concluded with a group photo session and followed by National Anthem. Inaugural function ended with a lunch break followed by Poster session.

Session III was started with the invited talk by Dr. Abhay Kumar Pandey from Allahabad University, Allahabad on the topic "Management of oxidative stress induced health effects by natural products". He spoke about the Oxidative stress and many plant extracts, phytochemicals that are frequently used to treat variety of clinical conditions associated with oxidative stress. It was followed by an invited lecture from Dr. B.S. Shankaranarayana Rao from National Institute of Mental Health and Neuro Sciences, Bengaluru on "Innovative Strategies to Treat Depression-induced Cognitive Deficits".

He demonstrated that depression causes impairment in spatial learning, alters the levels of monoamines and their metabolites and also suppresses hippocampal long-term potentiation (LTP) and enhances anxiety-like behaviours. Dr. Alpana Sharma from AIIMS, New Delhi spoke on "Surveying the crossroads of T cell biology in the immunopathogeneis of Pemphigus Vulgaris". In her presentation, she talked about Pemphigus Vulgaris (PV), a severe form of autoimmune skin disorder caused due to formation of auto reactive antibodies against the Desmoglein-3(Dsg3) of the keratinocytes. She said that T-helper 17 (Th17) and T-regulatory (Treg) cells play crucial role in regulating immune homeostasis in autoimmune disorders. In this maiden endeavor she studied the imbalance of Th17/Treg cell axis with possible involvement of their specific chemokines receptors (CCR) and ligands (CCL) in immunopathogenesis of PV. The next speaker Dr. Moinuddin from Aligarh Muslim University, Aligarh spoke on the topic "Glycoxidative modification of IgG renders it immunogenic with a possible role in rheumatoid arthritis". He explained Glycoxidation, non-enzymatic glycation and oxidation, which is a post-translational protein modification and results in the formation of advanced glycation end products (AGEs). Chairpersons of this session were Dr. B.S. Shankaranarayana Rao from National Institute of Mental Health and Neuro Sciences, Bengaluru & Dr. Huma Mustafa from CST U.P., Lucknow.

On 22nd July 2018 the day started with the session V. Chairpersons for this was Dr. Khursheed Alam from Aligarh Muslim University, Aligarh & Dr. Kalbe Jawad from UP University of Medical Sciences, Saifai, Etawah. Dr. Bechan Sharma from Allahabad University, Allahabad delivered a talk on "Therapeutic challenges in treatment of HIV infection: possible solutions". After the tea break, scientific session IV started with Chairpersons: Dr. Deepak Chandra from Lucknow University, Lucknow & Dr. Moinuddin from Aligarh Muslim University, Aligarh. Session started with invited talk by Dr. Anissa Atif Mirza from AIIMS, Rishikesh. She spoke on the topic "Preventing Gene Alterations is Main Mission and Vision of Every Human Being". She explained about prevention and protection of human genes by elimination and reduction of exposure of gene interacting agents. It was followed by invited talk by Dr. Sunil Babu Gosipatala from BBAU, A Central University, Lucknow. He presented the talk on topic "Regulatory role of HCMV miRNAs on Cellular Apoptosis". Human cytomegalovirus (HCMV), is a dsDNA (230-245Kb) virus causing significant morbidity and mortality in immuno-compromised individuals and neonates. Another invited talk was given by Dr. Kamla Kant Shukla from AIIMS, Jodhpur on topic "Effect of nutlin3 a in mice sperm via mitochondrial pathway". He explanined that nutlin 3 decreases the sperm motility and viability along with decreased gene expression of Bcl-2 and pro-caspase 3 on a dose- dependent manner.

Dr. Sanjay Mishra from IFTM University, Moradabad spoke on "In Silico Studies on Molecular Docking of Pyrimethamine Derivatives with Dihydrofolate Reductase in Plasmodium falciparum". He explored an effort for the design and development of the potent inhibitor for PfDHFR in view of controlling malaria. Dr. Rakesh Sharma from SIMS, Hapur delivered his talk on "Gluconeogenesis and oxygen status measurement in MCF-7 and PC-3 explanted tumors and metastasis grading by oncoproteomic painting". He reviewed about the feasibility of tumor multimodal integrated MRI/PET and MALDI image features with immuno-staining match as new approach of non-invasive real-time in vivo proteomic chemo-sensitivity biosensors to visualize anticancer action of anticancer drugs or cancer drug targeting. Session IV ended with dinner.

He described the application of antiretro-virals suppressing HIV-1 replication to undetectable levels exists in current chemotherapy.

This was followed by an invited talk by Dr. Nikhat Jamal Siddiqi from King Saud University, Riyadh, Saudi Arabia on "Alpha lipoic acid reduces acrylamide induced toxicity in rat brain". She said that Acrylamide treatment to rats caused a significant increase in brain protein and lipid peroxidation compared to control rats. Pretreatment with lipoic acid decreased the lipid peroxidation and restored the altered levels of reduced glutathione to almost normal values. Dr. Kausar Mahmood Ansari from CSIR-IITR, Lucknow spoke on "UVB irradiation-enhanced zinc oxide nanoparticles-induced DNA damage and cell death in mouse skin". He explained that UV-induced reactive oxygen species (ROS) have been implicated in photocarcinogenesis and skin aging. Session V ended with talk by Dr. Lakshmi Bala from BBD University, Lucknow on the topic "NMR metabonomics: a new approach reveals prognostic serum biomarkers for acute liver failure patients". She suggested that Proton nuclear magnetic resonance studies of serum have the potential of rapidly identifying patients with irreversible acute liver failure requiring liver transplantation as life saving option.

After the tea break, scientific session VI started. A talk delivered by Dr. Khursheed Alam from Aligarh Muslim University, Aligarh on "Deoxyribosylation of whole histone produces advanced glycation end products after going through multiple biophysical and biochemical changes".

He explained that Histones may quickly generate advanced glycation end products (AGEs) in presence of reducing sugars. The AGEs have been implicated in the pathogenesis and progression of many human diseases. Dr. Syed Shadab Raza from Era University, Lucknow spoke on "Chick embryo: A pre-clinical model to understand the ischemia-reperfusion mechanism". He described about disorders characterized by ischemia/reperfusion (I/R), such as myocardial infarction, stroke, and peripheral vascular disease.

This was followed by an invited Industrial talk (J&J) on "Improving Efficiency of Laboratory Services through Valu Metrix – Process Excellence". Dr. Neetu Singh from KGMU, Lucknow spoke on the topic "Dysbiosis and variation in predicted functions of the granulation tissue microbiome in HPV positive and negative severe Chronic Periodontitis". She presented retrospective analysis and correlation between severe Chronic Periodontitis (CP) cases with human papiloma virus (HPV). She aimed to explore deep-seated infected granulation tissue removed during periodontal flap surgery procedures for residential bacterial species between HPV +ve and -ve CP cases, which may serve as good predisposition marker for oral cancer. Chairpersons of this session were Dr. Neelam Sangwan from CSIR-CIMAP, Lucknow & Dr. Samir Sharma from Lucknow University, Lucknow. Session VI ended with a lunch break followed by Poster session.

After lunch break the conference commenced with session of oral and poster presentations by postgraduate students, residents, PhD scholars, postdoc and faculty members.

Conference included oral and poster presentations in which more than 60 scientific papers were presented. The two day National Conference of Central Zone of Association of Clinical Biochemists of India finally concluded on 22nd July 2018. Valedictory function was graced by Chief Guest Dr.Vineeta Das, Dean, Faculty of Medicine and Head, Department of Obs. & Gynae, King George's Medical University, Lucknow.

The function started with the welcome address by the Joint-Organizing Secretary Dr. Ranjana Singh. Thereafter, Vice Chancellor of Era University, Prof. Abbas Ali Mahdi addressed the gathering and highlighted the salient features and highlights of Central Zone ACBICON 2018.

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The awards for best oral and poster presentations were also distributed during the function. First prize for oral presentation was given to Dr. Babita Singh from KGMU, Lucknow who spoke on "Effect of Ethanolic extract of Bacopa monnieri against apoptotic pathways of dopaminergic neurons in Parkinson's disease" Second Prize was presented to Dr. Jamal Akhtar Ansari from KGMU, Lucknow who spoke on "GC-MS/MS and HPLC based identification of anticancer compounds from Zingiber officinale roscoe fraction ", and Third prize for oral presentation was presented to Dr. Mrinal Ranjan Srivastava from Era University, Lucknow on the topic "A study to compare efficiency of HbA1c, Fasting & Post Parandial blood glucose levels in the diagnosis of type II- diabetes mellitus and its prognostic outcome" and Dr. Sangeeta Singh from King George's Medical University, Lucknow for the presentation on "DNA methylation status of TGF- Beta 1 gene: A marker for T2DM associated nephropathy". The awards for best poster presentation were presented to:

Best Poster award-Day Ist: Hamda Khan, Integral University, Lucknow (Title: "Antiglycation activity of novel multimodal theranostic conjugate based on an anti-cancer fluorinated nucleotide conjugated with dual labelled albumin").

1) Sadhana Verma, Era University Lucknow (Title: "Anticancer and Antioxidant activity of Wheat grass on MCF-7 cell line").
2) Narottam Das Agrawal, Government Medical College, Jalaun (Orai) (Title: "Beryllium induced alterations in major metabolic pathways: Reversal by combination therapy of Aloe vera with Piperine").

Best Poster award-Day IInd:

1) Soumya Srivastava, KGMU, and Lucknow (Title: "Evaluation of miR-711 as a Novel Biomarker in Prostate Cancer").
2) Zeba Siddiqui, Integral University, Lucknow (Title: "Impact of in-vitro glycation of hemoglobin by D- ribose in neo-epitope generation and aggressive immune response").
3) Meenakshi Shukla, KGMU, Lucknow (Title: "Analysis of anti-proliferative activity of secondary metabolites of Tridax procumbens").

The valedictory function concluded with the vote of thanks by Dr. M. Kaleem Ahmad, Co-organizing secretary of Central Zone ACBICON 2018 followed by tea.

ACBI BENEVOLENT FUND

AN APPEAL

The Executive Council and GB were concerned to know the fact that one of our very senior members is suffering due to lack of money for his treatment and upkeep. For such situation many organizations have created 'Benevolent' fund to assist their members in dire need. We should also have compassion when any of our members are in need of help. Therefore the G.B. has decided to create a Fund to help our needy members and has sanctioned Rs. 50,000 from ACBI account for this fund. The IJCB Board has also decided to contribute Rs. 25,000. Many members have agreed to send money for the fund. Dr. B.C. Harinath has contributed Rs. 17000 which includes the money he got as recipient of ACBI-A.J. Thakur award for Distinguished Clinical Biochemist. Some have sent Rs. 1000 / 2000 /3000 as their contribution.

I solicit your support and appeal you to send money for this noble work as much as you like. The money is sent to the Treasurer, Association of clinical Biochemists of India, Biochem-Lab, East Boring Canal Road, Patna - 800001 by bank draft in the name of "ACBI Benevolent Fund" payable at Patna. The names of Donors are published in News Bulletin.

Dr. Rajendra Prasad

President

LIST OF DONORS TO ACBI-BENEVOLENT FUND

As on 25/09/2018

1	Association of Clinical Biochemists of India	50,000
2	Dr. B. C. Harinath, Prof. & Director, JBTDR Centre, Wardha	16,000
3	Dr. S. P. Dandekar, Prof. & Head, Department of Biochemistry, Seth G. S. Medical College, Mumbai	1,000
4	Dr. Sujata W., Biochemistry Deptt., PGI ,Chandigarh	1,000
5	Dr. K. P. Sinha, Retd. Professor of Biochemistry, Patna Medical College, & Advisor	1000
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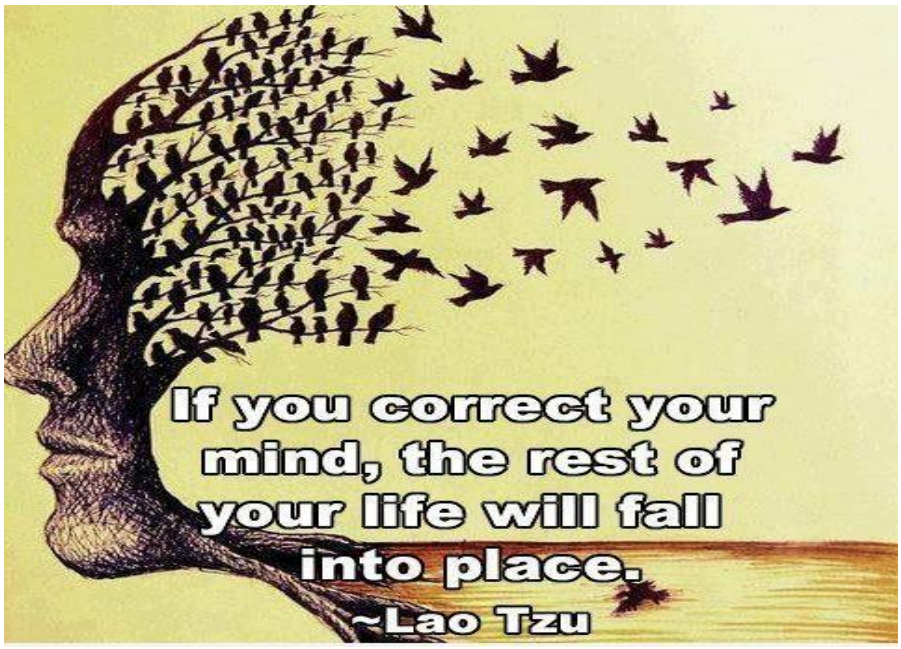
25	Dr. K. S. Gopinath – Bangalore	15000
26	Dr. Jayshree Bhattacharjee – Delhi	10000



ASSOCIATION OF CLINICAL BIOCHEMISTS OF INDIA
MEMBERSHIP APPLICATION FORM

(Please write in Capital or Type)

Please Affix Stamp-size Photograph here

1. Category of Membership Applied **(tick the choice)**: **Life/Associate Life/Annual/ Sessional**

2. Name **Dr/Mr./Mrs./Ms. :** .....

Family Name First name

3. Sex: ..... 4**.** Date of Birth: ..... 5. Nationality: .....

6. Academic Qualifications with Year: **(attach Photocopies)** .....

7. Designation : .....

8. OFFICIAL ADDRESS: .....

1. Department : .....

2. Institution: .....

3. Address : .....

.....

3. City: ..... 4. Pin Code: .....

5. State: ..... 6. Telephone (with area code): .....

7. Fax (with area code): .....

8. E-mail **(CAPITAL)** 9. Mobile .....

9. RESIDENTIAL ADDRESS:

1. Address: .....

2. City: ..... 3. Pin Code : ..... 4. State : .....

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6. Fax (with area code) : .....

7. E-mail (CAPITA) ..... 8. Mobile .....

10. Address for Communication: Official **OR** Residential **(please tick the choice)**

11. Professional Experience (briefly) on separate page: Teaching/Research/Diagnostic:…….Years

12. Field of expertise/ Areas of Interest: **(1)** ..... **(2)** .....

13. Publications, if any: **Attach a list giving details of publications.**

14. Membership of other professional bodies, if any : .....

15. Any other relevant information (brief): **(on separate page)**

16. D.D. No. ..... Date: ..... Bank : _____

Branch : ..... Amount: **Rs.** .....

(Enclose the crossed D.D. for an appropriate amount drawn in favour of **"Association of Clinical Biochemists of India"** payable at **Patna)**

Undertaking by the Applicant

I have gone through the bylaws of the Association of Clinical Biochemists of India. If admitted as a member, I shall abide by the rules and regulations of the association.

....

Signature of the Applicant Date Place

Recommendation by a member of ACBI (This is essential)

I have verified the information given in these applications that are true to the best of my knowledge. He/She fulfils eligibility requirement for becoming a member of ACBI. I recommend that ..... be accorded the membership of the ACBI.

Name & Signature of the Member. ..... Date: .....

ACBI Membership No.: ..... Place: .....

(Disclaimer)

I have no objection / I object* if my address and full details are put on the ACBI website at www.acbindia.org.

Signature of Applicant Date……..

* Strike out whichever is not applicable

ADMISSIBILITY RULES

ELIGIBILITY CRITERIA : Membership of the Association is open to teachers & research scientists in the discipline of Biochemistry, Clinical Biochemistry, Immunology, Pathology, Endocrinology, Nutrition, Medicine and other allied subjects in a medical institution and also to persons holding M.B.B.S., M.Sc.(Biochemistry or Clinical Biochemistry) and are engaged in research or practice of clinical Biochemistry in hospital or in private laboratory.

ASSOCIATE MEMBERSHIP: Those graduates who do not fit in the above criteria, but have an interest in Clinical Biochemistry are eligible to become Associate Members.

CORPORATE MEMBERSHIP: A company dealing in biochemical and instruments for biochemistry laboratories can become corporate members.

SESSIONAL MEMBERSHIP: Those persons who are not members but want to attend ACBI National Conference and attend and/or present papers have to become Sessional Member. This membership will be valid for that conference only. If he/she fulfils all eligibility criteria for membership and again pays the next year's Annual membership fees, they will be admitted as Annual Member of ACBI.

MEMBERSHIP FEE: (a) Annual Member – Rs. 600/- annually, **(b) Life Member – Rs.5130/- (Rs.5000**/- once **+** Rs.30/- for L.M.certificate posting + 100/- I Card **(**or Rs. 1800/- annually for 3 consecutive years.) **(c) For persons residing in other countries –** US $200/- **(d) ASSOCIATE LIFE MEMBERS - Rs.5130/- (Rs.5000**/- once **+** Rs.30/- for L.M.certificate posting + 100/- I Card**, (e) Corporate Member:** Rs. 25,000/- onetime payment. **(f) Sessional Member –** Rs. 600/- (**g) IFCC subscription (optional) -** Rs. 1500/- once.

Prescribed fee should be paid by **BANK DRAFT (Preferably on SBI)** only payable to **"ASSOCIATION OF CLINICAL BIOCHEMISTS OF INDIA"** at **PATNA. NO CHEQUE PLEASE. Our Bank – SBI, Patna Main Branch, West Gandhi Maidan, Patna, Bihar.** The completed application (along with enclosures) & draft should be sent to **Dr. Rajiv R. Sinha, General Secretary, ACBI, Biochem-Lab, East Boring Canal Road, Patna – 800 001,** preferably by registered post**..**

PHOTOGRAPH: Please affix a passport-size photo on the form.

PROFORMA

Members Identity Card

Please type or write in CAPITAL Letters.

1. Name: …….
2. Qualification: ……..
3. Membership Type : **LIFE / ASSOCIATE LIFE / CORPORATE / HONORARY**
   (will be filled up at Head office)
4. ACBI Membership Number: ……. …… (Will be filled up at Head office).
5. Work Place (City):……
6. State:……..
7. Date of Joining ACBI: ……will be filled up at Head office).

Please affix
Stamp size
Photograph.

(Do not staple or pin)

NEW MEMBERS: Filled up form to be posted along with the Membership application form. ID card charge is included in LIFE/ASSOCIATE LIFE/CORPORATE membership fees.

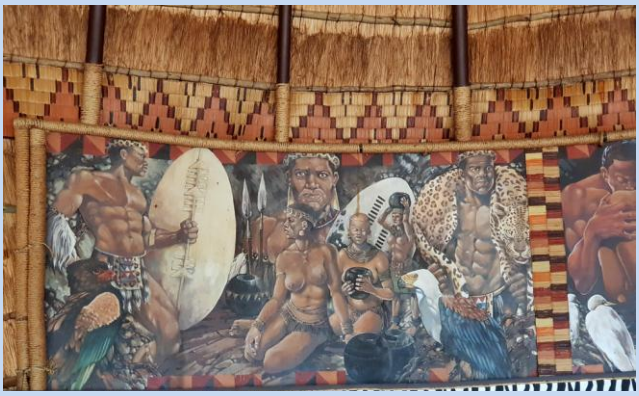
ALREADY A LIFE/CORPORATE MEMBER: Kindly fill up the form, paste one photo and send along with DD of Rs.100/-

Please Note:

Photo Identity card of ACBI is mandatory for members to attend the Annual Conferences, all meetings and also for exercising their voting rights. The charge for the ID card is Rs.100/-. Payment to be made by Demand Draft to "Association of Clinical Biochemists of India" payable at "PATNA".


CLINICAL DIAGNOSIS
R. SINHA


• Under the hypothesis that the G-308A polymorphism in the promoter region of the tumor necrosis factor alpha gene might increase tumor necrosis factor alpha expression, several investigations have been performed to examine the influence of the -308A allele on the risk of cardiovascular events.
• The results of these studies, however, have been conflicting.
• Results suggest that the G-308A polymorphism is unlikely to be associated with the development of IHD, whereas it might be a protective factor for ischemic stroke in Asians only.
K. VAIDYANATHAN

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