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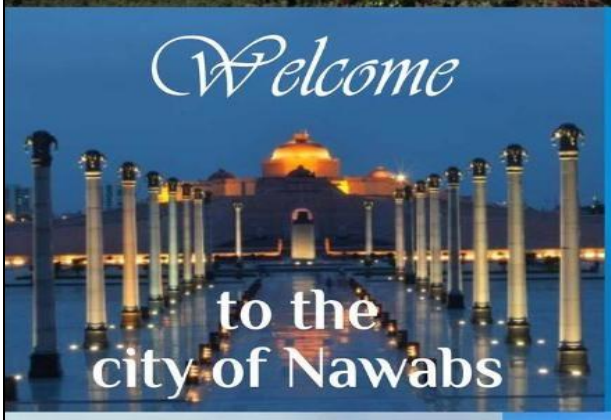

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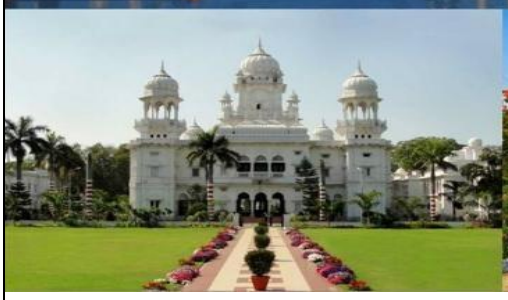

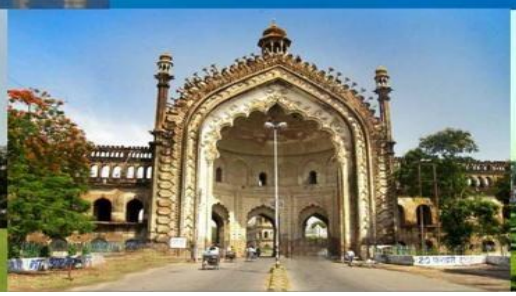

Pre-Conference Workshops & CME:
3rd December, 2017
Conference:
4th - 6th December, 2017
Venue:
Scientific Convention Centre,
King George's Medical University, Lucknow

Theme:
Emerging Trends in Clinical Biochemistry:
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Editorial

Dear Members,

Greetings.

The month of December will see Dr Abbas A. Mahdi welcoming you all to the city of Nawabs, Lucknow from 3rd. to 6th December 2017 as the host of the 44th Annual national Conference of ACBI. Dr. Mahdi has lined up a feast both for your brain & for your Stomach !!

As you all might be aware, your association had started the "ACBI BENEVOLENT FUND" to provide some financial help to members who may be in dire need of help. This is an appeal to all members of this association to contribute generously to this fund. Let the Good Samaritan in you shine out !!

Looking forward to meeting you all in Lucknow.

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 Meting & other sub-committees meetings	December 03, 2017 4.00 to 5.00 pm	KGMU, Lucknow
Pre GBM EC meeting	December 3, 2017 5.00 to 8.00 pm	
		KGMU Convention Centre
General Body Meeting		
Post GBM EC meeting	December 6, 2017 8:00 – 9:00 am (breakfast)	

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 CORRECTION FORM ,** fill it up and email the same to kpsacbi@yahoo.co.in.

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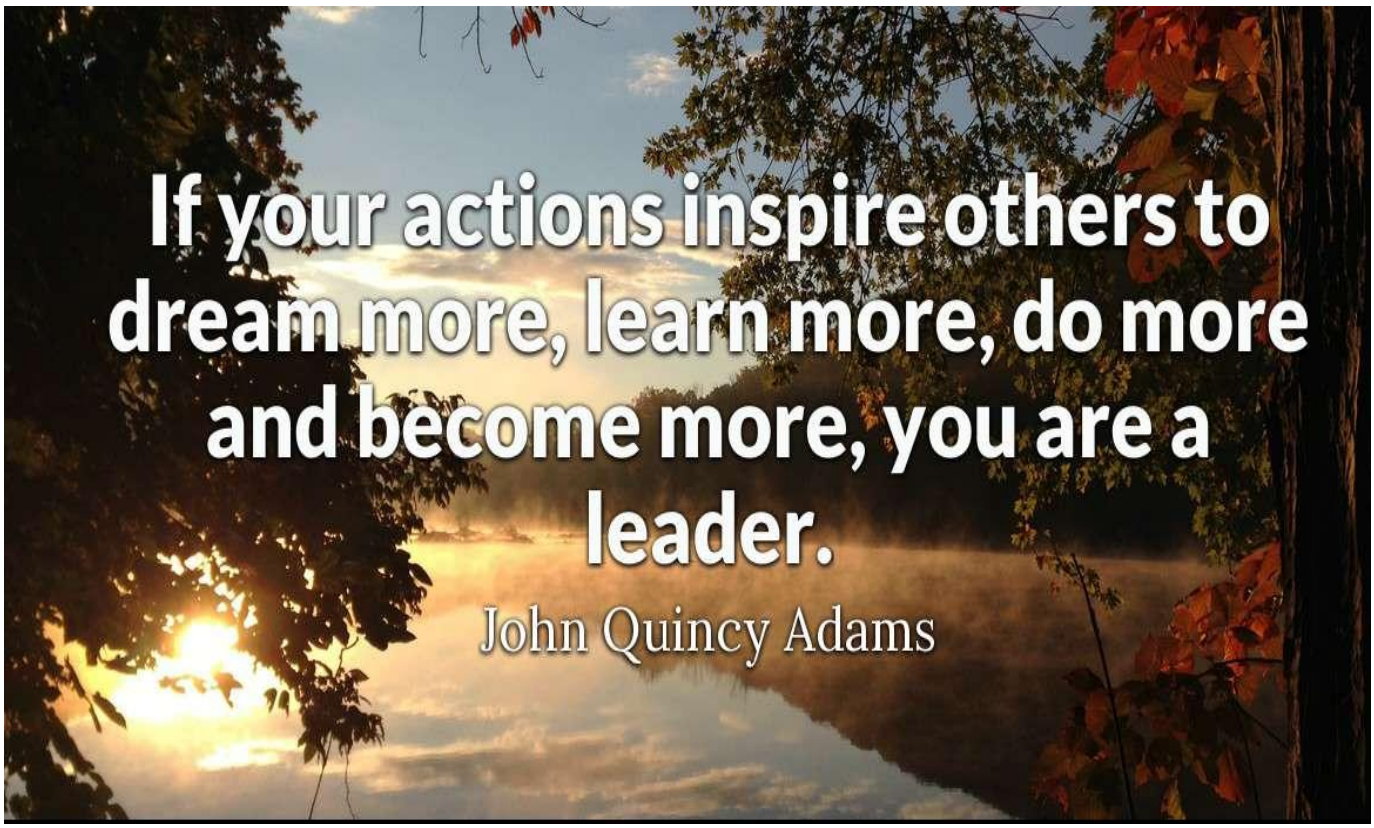

ARTICLE COURTSY eJIFCC

eJIFCC 2017 Vol 28 No2 pp122-133: ***Advances in the diagnosis of sepsis***

Nonconventional markers of sepsis

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INTRODUCTION

Although sepsis is one of the oldest syndromes in medicine it is a challenging healthcare problem even nowadays. In spite of the era of modern antibiotics and intensive therapy sepsis is still one of the leading causes of morbidity and mortality (1).

Sepsis is a heterogeneous and complex syndrome with various etiology, severity and prognosis. To our present knowledge the inflammatory response is the key role in the pathophysiology of sepsis however; a kind of uncertainty exists regarding the factors most likely to lead to increased lethality. In spite of the uncertainties one fact is obvious: the earlier the diagnosis of sepsis is raised, the more favorable outcome may be predicted (2, 3).

Based on the novel results and advances of pathobiology, management and epidemiology of sepsis, the definitions of the syndrome have been changed recently. Sepsis-3 consensus defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection (4).

The diagnosis of sepsis is most often not easy especially in newborns or in patients whose immune response is not adequate. Therefore, it is of utmost importance to introduce diagnostic biomarkers which can predict or verify systemic inflammation as early as possible. These tests should also be applicable for monitoring of the disease progression and efficacy of therapy as well.

Microbiological identification of pathogens is essential for efficient therapy of sepsis, because the clinical signs are nonspecific. Gold standard microbiological culturing methods require quite a long time (days), but new molecular biological techniques, polymerase chain reaction and mass spectrometric methods can shorten pathogen identification in the bloodstream (5). However, these methods can not differentiate between colonization and infection, moreover they need a well trained and equipped laboratory.

The diagnosis and monitoring of sepsis is of utmost importance, in this regard objective laboratory tests may provide rapid information for proper decision making. Up to now, more than 200 sepsis biomarkers have already been studied, most of them belonging to the inflammatory mediators' family (acute phase proteins, cytokines, chemokines, CD markers, adhesion molecules, etc.) (6, 7).

This mini review discusses classical sepsis biomarkers as well but the major focus will be on some of novel interesting nonconventional markers of sepsis.

CONVENTIONAL SEPSIS MARKERS: SERUM PCT AND CRP

The diagnostic and therapeutic guidelines of sepsis management recommend the use of procalcitonin (PCT) and C-reactive protein (CRP) measurements for early recognition of the syndrome (2, 8).

Blood levels of PCT rise 4-6 hours after the onset of systemic infection and PCT's half-life is about one day. Procalcitonin concentrations showed good correlation with the severity of sepsis, higher PCT levels correlated with higher risk of mortality (9). Massive tissue damage could also provoke elevated serum PCT values without infection, but fungal and viral infections do not elevate the PCT concentrations (10). Monitoring of PCT kinetics is recommended because delta PCT is a better marker of infection than absolute levels and furthermore, early PCT kinetics could indicate the efficacy of antibiotic therapy (11, 12).

CRP is a non-specific inflammatory marker, therefore it increases in many acute and chronic diseases (tissue injury, autoimmune disorders, malignancies), however in sepsis management, CRP could supplement PCT measurements. After infections serum CRP reaches its maximum within48-72 hours. Strongly elevated CRP levels were found to be severity and mortality predictors in sepsis (13). The measurement of high sensitivity CRP (hsCRP) is recommended.

Since both biomarkers have some limitations, promising other possibilities should be searched for and in fact, are available nowadays.

PRESEPSIN

CD14 molecule is a pattern recognition receptor existing in two forms: as a membrane-bound type (mCD14) and a soluble form (sCD14). Both forms play a role in recognition of LPS and in cell activation. Soluble CD14 subtype (sCD14-ST) also called as presepsin elevates significantly during inflammation and seems to be usable in differentiating between bacterial and nonbacterial infections (14).

Presepsin is normally present in very low concentrations in the serum of healthy individuals. In response to bacterial infections, its concentration increases within 2 hours, according to the severity of the disease (15). Studies have been reported with various diagnostic cut-off levels for sepsis between 400–600 pg/ml (16, 17). Preliminary studies showed that plasma presepsin is a highly sensitive and specific marker of sepsis, and its concentration significantly correlates with the severity of the disorder and in-hospital mortality of patients suffering from severe sepsis and septic shock (18). A novel point of care test is available on the market for rapid presepsin determination, which can help clinicians in rapid decision making.

Due to its 13 kDa molecular weight, presepsin is filtered through the glomeruli, then reabsorbed, and catabolized within proximal tubular cells (19). There is increasing evidence, that presepsin levels are affected by kidney function. Elevated presepsin levels were found in patients with decreased renal function and inverse correlation was described between presepsin and GFR as well (19, 20).Therefore, presepsin levels should be interpreted more attentively in patients with kidney disease.

ACTIN

Actin is a multifunctional 43 kDa protein which is present in all eukaryotic cells in monomeric/ globular (G-actin) and in polymeric/filamentous (F-actin) form (Figure 1). The two forms dynamically change due to the very rapid polymerization and depolymerization of the molecule. Actin takes a pivotal part in many cellular processes (building up microfilamental cytoskeleton, motility, moving, division, junctions) and in muscle contraction, too (22).

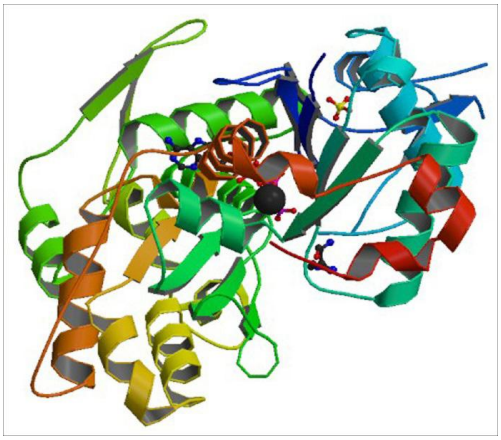
As actin is one the most abundant intracellular protein, during massive cell injury and catabolic conditions high amounts of actin can release into the circulation. Free extracellular actin has toxic effects, since actin filaments are thought to increase blood viscosity, to activate platelets, and cause endothelial cell damage and small blood vessel obstructions. Therefore, high amounts of extracellular actin may contribute to the development of multiple organ failure (23, 24).

The so called actin scavenger system is responsible for the protection of the body from actin toxicity; however the capacity of this defense system can be overwhelmed by massive tissue injury (25)

In healthy individuals the major source of extracellular actin is most probably the skeletal muscle with its large mass and high actin content. Circulating actin levels might provide clinically relevant information on disease severity, serum actin (se-ACT) levels were found to be higher in septic patients (3.5 (1.6-6.1) mg/L) than in controls (3.0 (2.1-3.7) mg/L) however did not meet criteria for statistical significance (Figure 2A). The cause of increased se-ACT levels in systemic inflammation and in sepsis might be the extensive tissue injury and detritus of blood cells (26).

There is only scarce data on urinary appearance of actin, however due to its molecular weight free actin could be filtrated through the glomeruli. Recently, our research group has observed the presence of actin in urine samples of septic patients in contrast, actin could not be detected in urine specimens from healthy individuals (27). Urinary actin (u-ACT) levels were determined by quantitative western blot, as in serum. Significantly higher urinary actin was measured in samples of patients with sepsis-related acute kidney injury (AKI, Figure 2B) compared to non-AKI patients (8.17 (2.09-45.53) ng/mL vs. 4.03 (091-10.21) ng/mL). Dialyzed patients showed extremely high u-ACT levels (36.02 (4.7-176.56) ng/ml). U-ACT correlated significantly ($p<0.01$) with kidney function markers (serum creatinine: 0.315, urinary albumin: 0.704) but no correlation was found with se-ACT levels (27).

Previously Kwon et al. found increased u-ACT levels as predictors of kidney failure after ischemic injury in renal allografts (u-ACT/u-Cr were 1095.6 ± 729.6 ng/mg in cadavers with sustained acute renal failure and 355.0 ± 247.0 ng/mg in cadavers recovering from acute renal failure; $p<0.05$) (28). However the appearance of actin in urine has not been clarified, u-ACT excretion may reflect overall cellular damage in the kidneys, thus it might provide novel possibility for early diagnosis of AKI, which is the most severe complication of sepsis.



The structure of native G-actin

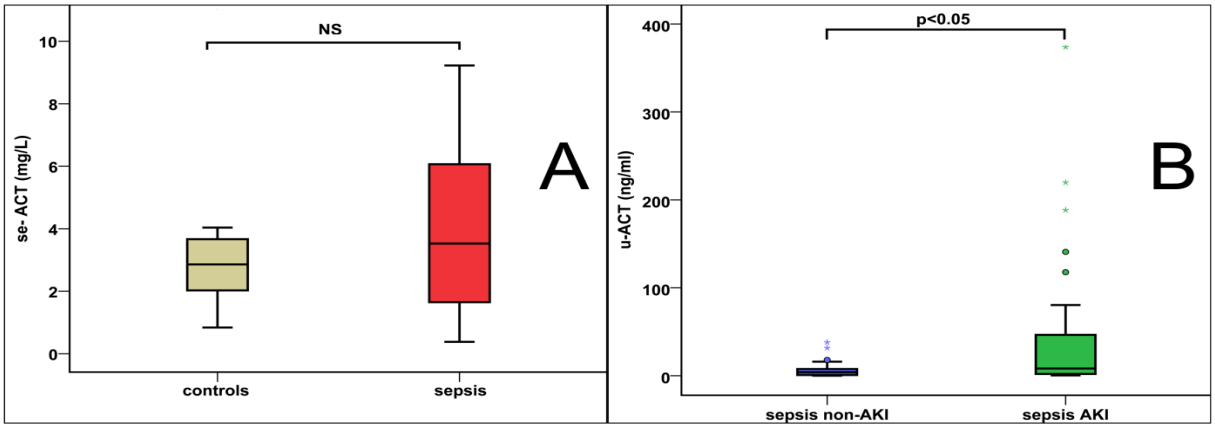


Figure : 2 Serum and urinary actin levels in septic patients

ACTIN-BINDING PROTEINS

In order to protect the body from overwhelming actin toxicity, there are two major extracellular actin-binding proteins called gelsolin (GSN) and Gc-globulin (group specific component, also called vitamin D-binding protein) (Figure 3). Both plasma proteins are essential actin scavengers working in concert. GSN severs and depolymerizes actin filaments originating from disrupted cells, and Gc-globulin frees GSN from actin monomers and sequesters them. The bound actin filaments and monomers are finally cleared from the circulation by the reticulo-endothelial system (31). Furthermore, both GSN and Gc-globulin could modulate inflammatory processes. Under physiological conditions, the concentration of actin in the blood is far less than that of actin binding proteins. Interestingly, in case of severe systemic inflammation, due to excessive tissue injury the excessive amount of extracellular actin and the pro-inflammatory mediators exceed the binding capacity of the scavenger proteins, so the plasma concentration of these drops significantly (25). Both actin-binding proteins are cleared from the circulation by the reticulo-endothelial system, however urinary levels of them are also studied (31).

GELSOLIN

Gelsolin is a ubiquitous, multifunctional protein. Three different isoforms exist in humans, two cytoplasmic forms and one circulatory isoform (32). Circulatory GSN is mainly secreted by muscle tissue (26). Circulatory GSN is a 93 kDa Ca2+- dependent protein and its plasma values range between 190-300mg/L (but these are highly method-dependent) (31,32). Besides actin, plasma GSN may also be able to bind to bioactive molecules (lysophosphatidic acid, sphingosine 1-phosphate, fibronectin and platelet activating factor), pro-inflammatory mediators and bacterial wall components (lipoteichoic acid and lipopolysaccharides). In follow-up studies, first-day GSN levels were proven to have a significant distinguishing ability regarding the septic and the non-septic states furthermore, GSN also predicted the outcome of sepsis (26, 34-36). Non-survivor septic patients showed lower levels of serum GSN (Figure 4). Recently, our research group introduced a new promising marker besides GSN, the serum actin/ GSN ratio (derived from the same patients' actin and GSN levels) which had similar prognostic value as APACHE II clinical scores regarding intensive care unit mortality (26). One limiting factor is the lack of a rapid detection method for actin and GSN, which is the current focus of our research.

Higher plasma GSN levels seem to have good prognostic value in sepsis, moreover the protective role of GSN have been proven by administration of exogenous gelsolin to rodents with septicemia and severe injury yielding reduction in mortality (37).

Studies regarding urinary GSN (u-GSN) levels in sepsis have been scarcely performed. Ferreia et al. (38) described u-GSN as a discriminating protein regarding cisplatin- and gentamicin-induced AKI in rats. Another study of Maddens et al. (39) reported increased u-GSN levels in septic mice. Both of these observations based on Western blot analyses indicated that u-GSN originates from the blood by glomerular filtration. In addition, u-GSN seems to be a possible diagnostic marker in patients suffering from type I diabetes mellitus (40). Interestingly, decreased u-GSN levels were found in rheumatoid arthritis patients (41), however they did not offer any predictive value. So far, all studies regarding u-GSN are promising starting points and should be further validated

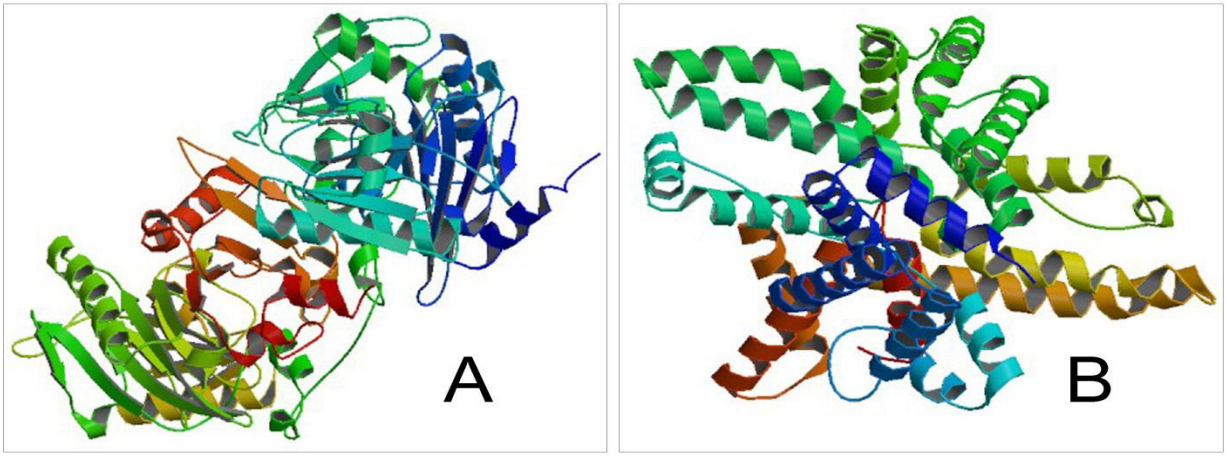
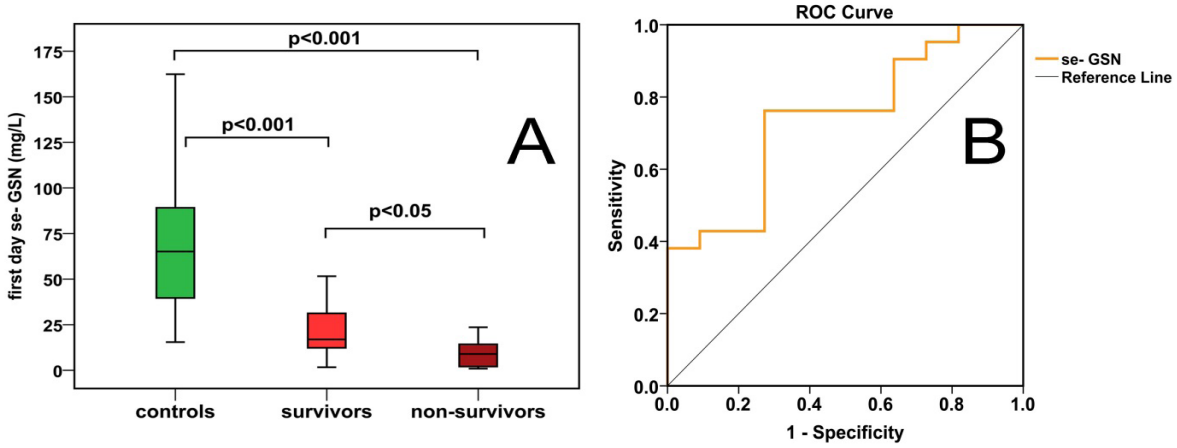


Figure : Crystal structures of calcium-free human gelsolin and that of uncomplexed Gc-globulin

A: GSN consists of six domains (G1-G6) indicated by different colors. In the Ca-free, inactive form of GSN, the six similarly folded domains adopt a compact globular structure held together by extensive noncovalent interactions of G2 with both G6 and the C-terminal tail (29).

B: Gc-globulin is built up of 3 three homologous α-helical domains. Domains I and II can be subdivided further into two structurally related subdomains (30).

Figure : A: First-day serum GSN levels in septic survivor and non-survivor patients based on 7-day mortality
B: Receiver operating characteristic curve of serum GSN for predicting 7-day mortality of sepsis



AUC: 0.74, cut-off value: 11.38 mg/L (sensitivity: 76.2%, specificity: 72.7%). Based on (26).

GC-GLOBULIN

Plasma Gc-globulin (52 - 59 kDa) is a member of the albuminoid superfamily. Gc-globulin is mainly produced by the liver (serum level: 300- 600 mg/L) owning 3 major isoforms (Gc1f, Gc1s, Gc2) (42). Gc-globulin seems to act as an acute-phase protein after injury. Also, important function of Gc-globulin is binding and transporting 25-OH-D and 1,25-(OH)2D3 vitamin metabolites. Furthermore it enhances neutrophil chemotaxis and could modulate T cell responses (42).

Admission plasma concentration of Gc-globulin below 134 mg/L (determined by immune nephelometry) was found to be associated with organ dysfunction (hematologic or respiratory failure) and sepsis after traumatic injury (43). Jeng et al. found an association between critical illness and lower 25-OH-D and Gc-globulin levels in critically ill patients when compared to healthy controls (44).

Gc-globulin is filtered freely through the glomeruli because of its low molecular weight. In the kidney, Gc-globulin is involved in the vitamin D biosynthesis process. Under normal circumstances, Gc-globulin is reabsorbed and catabolized by proximal tubular epithelial cells resulting only in a trace urinary excretion (42).

Therefore, acute tubular injury is expected to result in exaggerated urinary Gc-globulin excretion. Recently, urinary Gc-globulin (u-Gc-globulin) was reported as a promising novel biomarker of major contrast material induced nephropathy-associated events (u-Gc-globulin/u-Cr in patients developing major adverse renal events (MARE) vs. those without MARE were 125.68 ± 211.62 vs. 14.99 ± 38.10 ng/ml/mmol/l; $p<0.001$) (45). Shoukry et al. have determined increased u- Gc-globulin levels by ELISA in diabetic patients as an early diagnostic marker of diabetic nephropathy. Urinary Gc-globulin/u-Cr levels were
patients compared to controls (1516.3 ± 228.6 ng/mg vs. 123.4 ± 28.2 ng/mg; $p<0.001$) (46). Investigating the association between sepsis-induced acute kidney injury and Gc-globulin in urine still remains an interesting challenge.

OROSOMUCOID

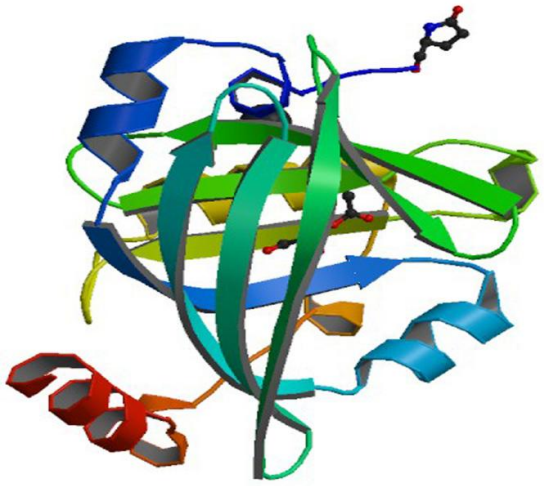
Orosomucoid (ORM) or α-1-acid glycoprotein is a positive acute phase protein. ORM is a 41-43kDa heavily glycosylated protein (Figure 5) with several transport and immunomodulatory function (47). ORM has been described as part of the non-specific defense system against excessive inflammatory response (48). ORM has anti-neutrophil and anti-complement activity, it can inhibit apoptosis, macrophage activation, lymphocyte proliferation, superoxide generation, and platelet aggregation as well (49). Its protective role was demonstrated also in several rodent models of shock, inflammation and sepsis (50-52).

The normal orosomucoid concentration in human serum ranges between 0.5-1.2 g/L and it can rise during acute and chronic inflammatory diseases (53). In spite of the well-known fact that serum orosomucoid (se-ORM) is a non-specific inflammatory marker, recently it has been described as a potential diagnostic and prognostic biomarker of sepsis. Significantly higher levels were found in sepsis than in SIRS and admission se-ORM levels showed a good prognostic accuracy for sepsis mortality if combined with SOFA score (AUC ROC: 0.878) (54). ORM is also present in urine, but with much lower concentrations than in serum, normally ORM accounts for about 1-5 % of total proteins in urine (<3 mg/L) (55, 56). Previous studies described slightly elevated u-ORM levels in diseases associated with chronic inflammatory activation, like autoimmune diseases, diabetes mellitus and cancer (57-60). U-ORM excretion can be elevated after acute inflammatory stimuli as well. Recently published data suggest that u-ORM could be a promising non-invasive marker for diagnosis of sepsis (61). About 100-times higher levels were found in sepsis than in controls, and SIRS patients showed 10-fold higher u-ORM levels than controls. U-ORM was referred to urinary creatinine levels and a cut off value at 6.75 mg/mmol with great sensitivity and specificity (94.7% and 90.0%, respectively) has been described for diagnosis of sepsis. The diagnostic accuracy of u- ORM for sepsis (AUC ROC: 0.954) was similar to PCT and higher than se-ORM. Furthermore, u- ORM levels correlated well with conventional inflammatory parameters. In this study, extremely elevated u-ORM levels were found in septic patients with dialysis requirement (61). Another paper demonstrated u-ORM above 40 mg/L as an early predictor for acute kidney injury after cardiac surgery in children (AUC ROC 0.87). U-ORM values were found to be strongly associated with severity of AKI (62).

In spite of the promising data, the exact mechanism of u-ORM elevation is not well explored. Local renal processes due to systemic inflammation could play a crucial role, since extrahepatic gene expression of ORM (leukocytes, endothelial cells, kidney, etc.) has been described (63). Furthermore, glomerular and tubular dysfunction also may have a pivotal part.

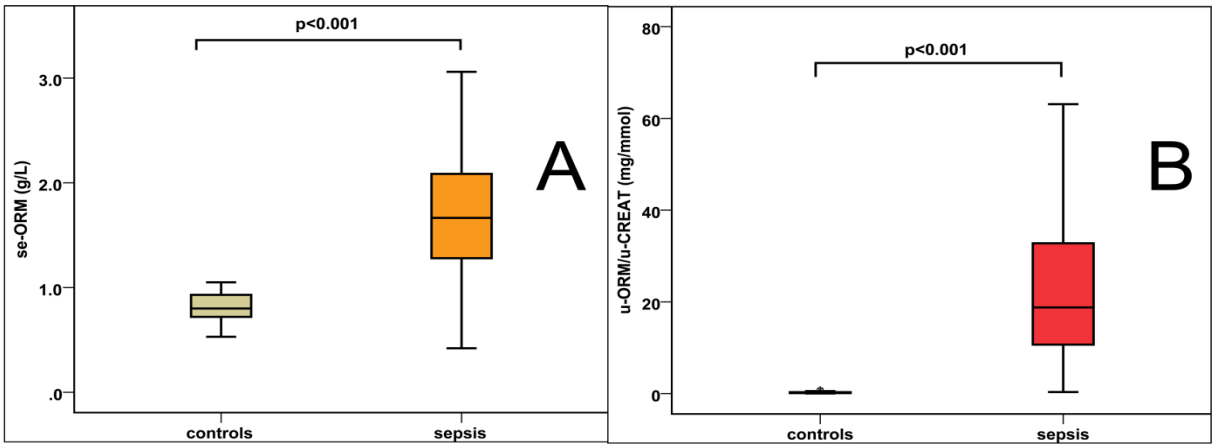
U-ORM seems to be a more sensitive marker of sepsis than se-ORM (Figure 6), providing clinically relevant information for real-time monitoring of inflammatory activation in a non-invasive manner.

Figure : Crystal structure of human orosomucoid (alpha1-acid glycoprotein)



ORM contains a typical lipocalin fold with an eight-stranded beta-barrel. This structure is responsible for diverse ligand-binding. Furthermore, ORM structure contains five N-linked glycosylation sites (47).

Figure 6 : Serum orosomucoid (A) and urinary orosomucoid (B) levels in sepsis



Urinary orosomucoid levels are referred to urinary creatinine and expressed in mg/mmol. Based on (61).

CONCLUSION

The outcome of sepsis largely depends on early diagnosis and the earliest possible beginning of a consecutive adequate antibiotic therapy. For definitive diagnosis, identification of pathogens is still the gold standard however this approach quite often requires several hours or days leading to a delay in decision making. Therefore, measurement of fast responding protein biomarkers of sepsis has gained a major focus in the last decades. Unfortunately, most of the protein biomarkers do not have proper specificity even if they possess better sensitivity. For the assessment of overall tissue damage, monitoring of the actin-scavenger system is a promising new entity. Urinary markers provide a non-invasive tool for real-time monitoring of septic processes. Orosomucoid determination in urine might be a novel possibility for the early recognition of systemic inflammation. Since sepsis is a heterogeneous clinical syndrome and not a definitive disease a single marker alone should never be satisfactory. Multi-marker approach and complex evaluation of the clinical signs and biomarkers should improve patient management at the bedside.

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FORTHCOMING EVENTS :

ACBI Election Notice

Call for Nominations to fill up vacancies in

Executive Council of ACBI – 2018.

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 :

Dr. Poornima Manjrekar
Professor & Head
Department of Biochemistry
Centre for Basic Sciences
Bejai
Mangalore -

The Last date for receiving the Nominations: November 15th, 2017

The Last date for withdrawal of Nominations: November 30th, 2017

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.]

Recurrent Nocturnal Hypoglycemia in a Patient with Type 1 Diabetes Mellitus

Tze Ping Loh, Shao Feng Mok, Shih Ling Kao, Eric Khoo, Ah Chuan Thai

DOI: 10.1373/clinchem.2013.214676 Published September 2014

CASE

A 39-year-old man with type 1 diabetes mellitus (DM) was admitted with diabetic ketoacidosis precipitated by an upper respiratory tract infection. His admitting biochemistry showed venous plasma glucose concentration of 933 mg/dL (51.8 mmol/L) [reference: 72–140 mg/dL (4.0–7.8 mmol/L)], bicarbonate of 14.7 mmol/L (22–31 mmol/L), β-hydroxybutyrate of >6 mmol/L (<0.6 mmol/L), and arterial pH of 7.28 (7.35–7.45). He was treated with intravenous hydration and intravenous insulin infusion, and made a rapid recovery.

The patient had been diagnosed with type 1 DM at the age of 33 years when he presented with diabetic ketoacidosis. Glutamic acid decarboxylase antibody was increased at the time of diagnosis [10.6 U/mL (reference: <1 U/mL)] and postprandial C-peptide concentrations were undetectable. His subsequent glycemic control was poor [glycated hemoglobin (Hb A_{1c}) ranged from 8.9% to 15.6%], which resulted in peripheral and autonomic neuropathy manifesting as painful sensory neuropathy and erectile dysfunction, respectively.

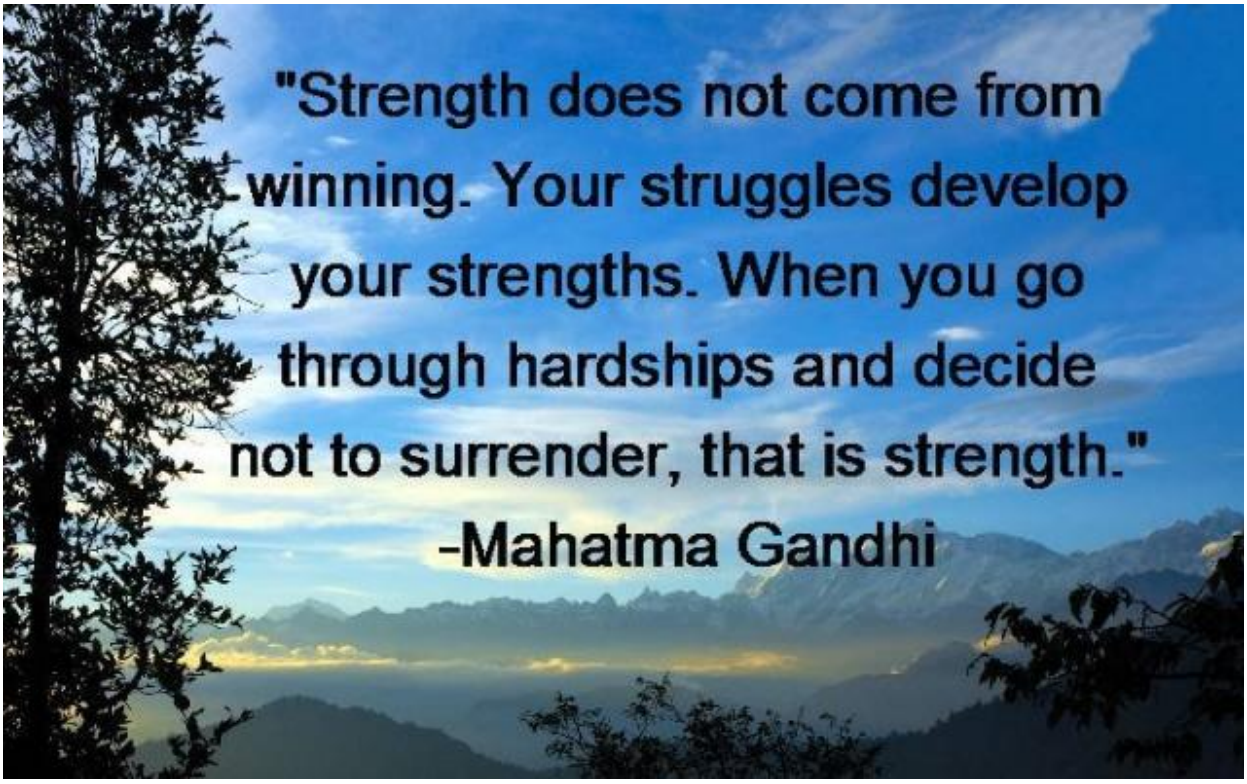
His other medical history included mitral valve prolapse, hypertension, and dyslipidemia. He was prescribed a basal-bolus insulin regimen consisting of twice-daily insulin detemir (10 U before breakfast and 7 U before dinner) and insulin aspart (5 U before breakfast, 3 U before lunch, and 4 U before dinner), simvastatin, sildenafil, pregabalin, and omeprazole. He was not prescribed sulfonylurea and denied alcohol consumption. After resolution of diabetic ketoacidosis, the patient was restarted on his preadmission basal-bolus insulin regimen. His insulin regimen was titrated during this hospital admission, and he had wide fluctuations in blood glucose and recurrent nocturnal hypoglycemia. Typically, there was severe hyperglycemia during daytime [capillary glucose: 205–553 mg/dL (11.4–30.7 mmol/L)], particularly after meals, and symptomatic hypoglycemia that consistently occurred between 2400 and 0230 daily [capillary glucose: 34–58 mg/dL (1.9–3.2 mmol/L)], accompanied by symptoms of adrenergic response such as diaphoresis, palpitations, and anxiety.

Physical examination revealed stable vital signs and low body mass index (16.4 kg/m^2). There was no abnormal hyperpigmentation typical of Addison's disease. The thyroid gland was not enlarged, and he was clinically euthyroid. Cardiovascular and respiratory examinations were unremarkable. There was mild lipohypertrophy at the insulin injection sites. Other relevant serum biochemistry results were albumin 4.0 g/dL (3.8–4.8 g/dL), aspartate aminotransferase 10 U/L (14–50 U/L), alanine aminotransferase 10 U/L (10–55 U/L), γ-glutamyl transferase 30 U/L (10–70 U/L), and creatinine 0.6 mg/dL (53 μmol/L) [0.7–1.4 mg/dL (65–125 μmol/L)]. Insulin and C-peptide concentrations measured at the time of 1 of the hypoglycemic episodes (venous glucose: 2.8 mmol/L) during this admission were 83.6 mU/L (0.0–25.0 mU/L) and 36 pmol/L (364–1655 pmol/L), respectively. He was biochemically euthyroid.

POINTS TO CONSIDER

1. What are the etiologies of recurrent hypoglycemia in patients on insulin therapy?
2. What is the suggested approach to recurrent hypoglycemia?
3. Can insulin antibodies cause hypoglycemia?

ANSWER WITH DISCUSSION ON PAGE: 26



NEWS FROM BRANCHES/ZONES

SOUTH REGIONAL CONFERENCE OF ACBI.

A National seminar on Lifestyle Diseases and Management was organized by the ACBI Kerala chapter, Council for Clinical and Diagnostic Professionals (CCDP) and Department of Biochemistry, Believers Church Medical College, in connection with the Southern regional conference of the ACBI at Believers Church Medical College Hospital, Thiruvalla, Pathanamthitta, Kerala, on 30th June and 1st July 2017. Hospital, Thiruvalla, Pathanamthitta, Kerala, on 30th June and 1st July 2017. The Seminar was inaugurated by Rt. Rev.Praison John, Believers Church. Dr. D M Vasudevan, chairman of the organizing committee and the past president of ACBI chaired the function. Dr. Subaida M R, Head, Department of Biochemistry delivered the welcome address. Rev. Fr. SijoPandapallil, Manger, BCMCH, Dr. John Abraham, Principal BCMCH, Dr. Mohan Varghese, Associate director, BCMCH, Dr. Kannan Vaidyanathan, organizing secretary and the ACBI south zone representative, and Dr. George, ACBI state representative, gave the felicitation. The proceeding of the seminar was released by Bishop Praison John, by presenting a copy to Dr. F S Geethanjali, Professor and HOD, Department of Clinical Biochemistry, CMC Vellore. During the function, the first eminent scientist award instituted by the CCDP, "Dr. T Vijayakumar eminent scientist award" was awarded to Dr. F S Geethanjali Professor and HOD, Department of Clinical Biochemistry, CMC Vellore. Mr. Riju Mathew, Manager, Laboratory gave the vote of thanks.

The inaugural session was closed by prayer and benediction by Rev. Fr. Daniel Johnson, Director, Medical missions.

The seminar started with a keynote address on Diagnostic Advances of Diabetes Mellitus and Complications by Dr D M Vasudevan. The Invited speakers were Dr. F S Geethanjali M.Sc.,Ph.D., Prof & HOD, Clinical Biochemistry, Christian Medical College Hospital (CMC), Vellore (Quality Control), Dr. Divya Pachat MD., PDF., Clinical Geneticist, MES Medical College, Perinthalmanna (Genetics from Bench to Bedside), Dr. Ravi Cherian, MD., DM (Cardiology)., Cardiologist, BCMCH (Dyslipidemia and Coronary Heart Disease : Lifestyle Approaches for its Management), Dr. P T Annamalai, Professor, Biochemistry, Jubilee Mission Medical College & Research Institute (Non Alcoholic Fatty Liver Disease - A Biochemist's Enigma), Dr. Mohan Varghese, MD, Senior Consultant & Diabetologist, BC MCH (Pre- Diabetes and Pre Hypertension), Dr. Mumthas P., DGO, DNB, Associate Professor, Dept. of OBG, MES Medical College, Perinthalmanna (Metabolic Syndrome : A Gynecological Perspective), Dr. Arunakaran Ph.D., Director, Research Meenakshi Academy Of Higher Education And Research (MAHER), Chennai (Life Style Diseases and Management), Dr. PadmajaHari MD., Professor, Department Of Physiology, Kovai Medical Hospital & Research Centre, Coimbatore, Pathophysiology of Metabolic Syndrome, Dr. George Chandy Matteethra MD.,DM(Gastro.)., Director& CEO, BCMCH (Lifestyle Diseases - GI and LIVER).

More than 250 delegates including post graduate students and faculty members participated in the seminar. The delegates included participants from Kerala, Tamil Nadu, Pondicheri, Karnataka and Andhra Pradesh. 20 abstracts were received of which the scientific committee selected 4 papers for oral presentation and 16 papers for poster presentation. For oral presentation the first price was won by Geena Augustine and the second prize by Mirshad P.V, both from Maher University Chennai.

Uma Subramanian Unni, Lynn Elizabeth Thomas, Manju Koshy of Believers Church Medical College and Riju Mathew of Yenepoya University shared the first price for the poster presentation. The second prize for poster was won by Sheena Joe of Maher University Chennai. Mr. John Gnanaharan invited the gathering for the next regional conference of ACBI to be conducted on 26-28 September, 2018, at KMC ,Manipal.

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 be 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 30. 8. 2016

1	Association of Clinical Biochemists of India	50,000/-
2	Dr. B. C. Harinath, Prof. & Director, JBTDR Centre, Wardha	16,000/-
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4	Dr. Sujata W., Biochemistry Deptt., PGI ,Chandigarh	1,000/-
5	Dr. K. P. Sinha, Retd. Professor of Biochemistry, Patna Medical College, & Advisor	1,000/-
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21	Dr. M. B. Rao – Mumbai	2,000/-
22	Dr. Praveen Sharma – Jodhpur	30,000/-
23	Dr. T. F. Ashavaid – Mumbai	10,000/-
24	Dr. K. S. Gopinath – Bangalore	15,000/-
25	Dr. Jayshree Bhattacharjee – Delhi	10,000/-
26	Dr. Manorma Swain, Cuttack	3,000/-

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 : .....
4. Academic Qualifications with Year : **(attach Photocopies)** .....
7. Designation : .....
8. OFFICIAL ADDRESS :

   1. Department : .....
   2. Institution : .....
   3. Address : .....
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   6. State : ..... 7. Telephone (with area code) : .....
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9. Address for Communication : Official **OR** Residential **(please tick the choice)**

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

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

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

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

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

15. 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 this application 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 years 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/- one time 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".

ANSWER & DISCUSSION

From Page : 18

CLINICAL CHEMISTRY CLINICAL CASE STUDY

Recurrent Nocturnal Hypoglycemia in a Patient with Type 1 Diabetes Mellitus

Discussion

Hypoglycemia is a common complication of insulin therapy in patients with DM, and is a barrier to the achievement of glycemic control. It causes significant physical and psychological morbidity and occasionally, mortality. The underlying cause of hypoglycemia should be evaluated and addressed to prevent recurrent episodes. Hypoglycemia in a patient with DM is most commonly caused by an absolute or relative therapeutic insulin excess. Causes of absolute insulin excess include excessive or ill-timed insulin secretagogue or insulin, or decreased insulin clearance as in renal failure; relative insulin excess occurs when the prevailing insulin is not matched by glucose delivery (exogenous), utilization, or production (**1**). Relative or absolute insulin excess is usually apparent from the history of events before the hypoglycemic episodes. A detailed history did not suggest insulin excess as a cause of the hypoglycemic episodes. The dose of insulin prescribed in this patient was matched to his calorie intake, and he was able to administer the prescribed dose accurately. He denied any surreptitious use of insulin. Lipohypertrophy at insulin injection sites can impair absorption and is another common cause of glucose fluctuations. This patient had only mild lipohypertrophy, and change of insulin injection site in this patient did not alleviate the recurrent hypoglycemic episodes. Hepatic and renal failure were excluded by clinical examination and aminotransferase activities and albumin and creatinine concentrations that were within reference intervals. Adrenal insufficiency, particularly coexisting Addison's disease in a patient with type 1 DM, can cause hypoglycemia. A short cosyntropin test produced a peak cortisol concentration of 34.8 μg/dL (960 mmol/L) [adequate response: >20.0 μg/dL (>550 mmol/L)] and excluded that diagnosis. The patient did not drink alcohol, and he was not on any other medications (apart from insulin) that could cause hypoglycemia. Diabetic gastroparesis (prevalence: 30–40% of DM patients) is a condition characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach owing to autonomic neuropathy (**2**). This condition may precipitate hypoglycemia, as delayed food transit causes a mismatch between insulin delivery and carbohydrate absorption. In view of the history of autonomic neuropathy and a history of recurrent sensation of bloating after meals, a gastric emptying study was performed on this patient and showed delayed emptying.

However, the pattern of hyperglycemia 2–3 h after meals (particularly postdinner) followed by hypoglycemia after midnight was not consistent with the pattern usually observed in gastroparesis.

Having excluded the more common causes of hypoglycemia in a patient with DM on insulin therapy, further investigations were undertaken to investigate other etiologies of the recurrent hypoglycemia. Insulin and C-peptide concentrations were measured during the episodes of hypoglycemia. Undetectable C-peptide concentrations during 3 separate episodes of hypoglycemia excluded endogenous hyperinsulinism, such as caused by insulinoma, as the etiology of recurrent hypoglycemia (**3**).

After excluding the above causes, antiinsulin antibodies (IAs) were considered, in view of the raised insulin concentration during episodes of hypoglycemia. Chronic use of exogenous insulin may give rise to IAs that may sequester insulin. Consequently, a larger dose of insulin analog may be required to overcome the binding capacity and allow sufficient free insulin to act peripherally. The free and bound insulin exist in equilibrium. As free insulin is metabolized, bound insulin will be released from IAs. This has an effect of retarding initial insulin action causing daytime hyperglycemia; conversely, the subsequent release of insulin from IA may cause nocturnal hypoglycemia, if the released insulin is not countered with calorie intake (**4**).

The IAs can be characterized by their binding capacity and affinity. Patients with low-capacity, high-affinity IAs typically do not develop hypoglycemia. In contrast, patients with moderate-capacity, low-affinity IAs may suffer from moderate nocturnal hypoglycemia. Patients with high-capacity, low-affinity IAs may suffer severe daytime hyperglycemia and nighttime hypoglycemia and may require treatment with immunosuppressants (**5**).

The IAs can be thought of as macroinsulin interference. However, unlike other macrohormone interference, evaluation of nonlinearity by dilution of patient samples or retesting of insulin on an alternate assay is not useful for investigating IAs in patients with DM on insulin therapy. This is because most insulin assays do not show linear recovery with insulin analog and have different cross-reactivity with insulin analogs (**6**). For this reason, assessment of underrecovery after adding insulin to the sample is probably also unreliable. Gel chromatography can be used to confirm the diagnosis of macroinsulin, and therefore presence of IAs, by showing an insulin peak in the immunoglobulin mass area (**7**).

IAs also can be directly measured. These assays are not routinely available in most laboratories. When IAs are suspected, measurement of free, direct, and total insulin concentrations are helpful. Direct insulin is the insulin concentration measured from the native patient sample. Free insulin is obtained by measurement of the supernatant after polyethylene glycol (PEG) precipitation. Total insulin is obtained by first adding acid to the patient sample to dissociate the antibody-bound insulin, followed by PEG precipitation and pH neutralization (**8**, **9**).

In health, the total, direct, and free insulin concentrations exist in ratios close to 1, as circulating insulin is not significantly bound by protein (**8**, **9**). A raised direct:free insulin or total:direct insulin ratio is suggestive of IAs. These ratios are assay specific (**8**, **9**). For this patient, the direct:free and total:direct insulin ratios were 1.03 and 0.98, respectively, using the Advia Centaur assay (Siemens Healthcare Diagnostics). Direct measurement of the IA concentration was 0.01 nmol/L (reference: ≤0.02 nmol/L, Mayo Medical Laboratories). These results excluded the diagnosis of IAs. As the cause of recurrent hypoglycemia remained unexplained, we measured 24-h insulin and glucose profiles of the patient.

The 24-h insulin profile showed an unexpected peak between 2400 and 0230 that coincided with severe hypoglycemia (1.9 mmol/L). This peak could not be explained by the prescribed insulin regimen of the patient (**Fig. 1**). We suspected that the peak represented surreptitious administration of a short-acting insulin analog. After the results of the 24-h insulin profile were explained to the patient, there were no further occurrences of nocturnal hypoglycemia. He was subsequently referred for psychiatric care and eventually disclosed several significant social stressors.

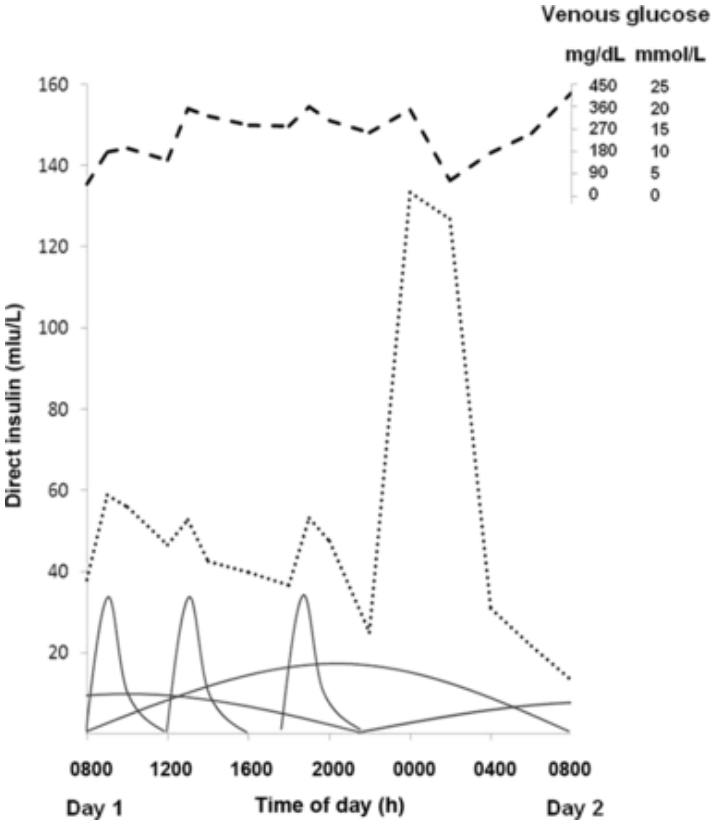

Fig. 1.The 24-hour insulin and glucose profiles of the patient.

The dashed line represents the venous glucose, the dotted line represents the direct insulin, and the solid lines represent the prescribed short-acting insulin aspart (narrower peak) and longer-acting insulin detemir (broader peak). There was a large insulin peak that did not correspond to any insulin injection and coincided with the hypoglycemic event of the patient. We concluded that this patient had factitious hypoglycemia, a syndrome where patients self-induce hypoglycemia to seek medical attention or assume a sick role.

It represents a significant diagnostic challenge and often goes undiagnosed for years in patients previously labeled with brittle diabetes (**10**). The clinical presentation often closely mimics genuine clinical conditions and patients often show concern about their condition and are keen for investigation and interventions. They often have a history of multiple admissions and visits to different institutions. This patient had been admitted to multiple local hospitals on 18 occasions over the last 2 years for recurrent hypoglycemia and noncrisis hyperglycemia.

It is important to recognize that this condition is a diagnosis of exclusion and should be made only after careful exclusion of potential organic causes to avoid inappropriately labeling the patient, which carries significant social, legal, and clinical implications. However, this should also be balanced against the need for early recognition to avoid unnecessary diagnostic and therapeutic interventions that are wasteful of resources and may bring harm to the patient. **Fig. 2** shows a suggested diagnostic approach to patients with recurrent hypoglycemia.

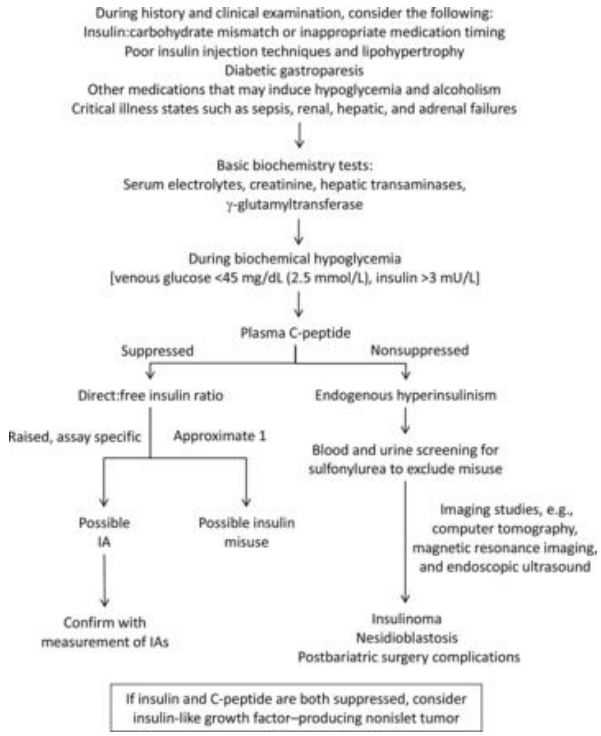

Fig. 2.A suggested approach to diagnosis of recurrent hypoglycemia in patients with diabetes mellitus.

POINTS TO REMEMBER

- Hypoglycemia in patients with DM is a common occurrence and is most commonly caused by an absolute or relative therapeutic insulin excess. Lipohypertrophy at the insulin injection site can impair insulin absorption and can cause glucose fluctuations. Delayed gastric emptying, caused by diabetic gastroparesis (30%–40% DM patients), can also cause hypoglycemia.
- Insulin antibodies and surreptitious use of exogenous insulin can produce inappropriately high concentrations of insulin during hypoglycemia.
- Factitious hypoglycemia is highly challenging to diagnose and manage. It should be considered as a differential diagnosis in unexplained hypoglycemia and is a diagnosis of exclusion.
- Measurement of C-peptide and free and direct insulin can help differentiate factitious hypoglycemia from other organic causes.
- A high insulin concentration with raised direct:free insulin ratio recorded during an episode of hypoglycemia suggests insulin misuse as the likely cause.

[Article courtesy CLINICAL CASE STUDY – *AACC*]


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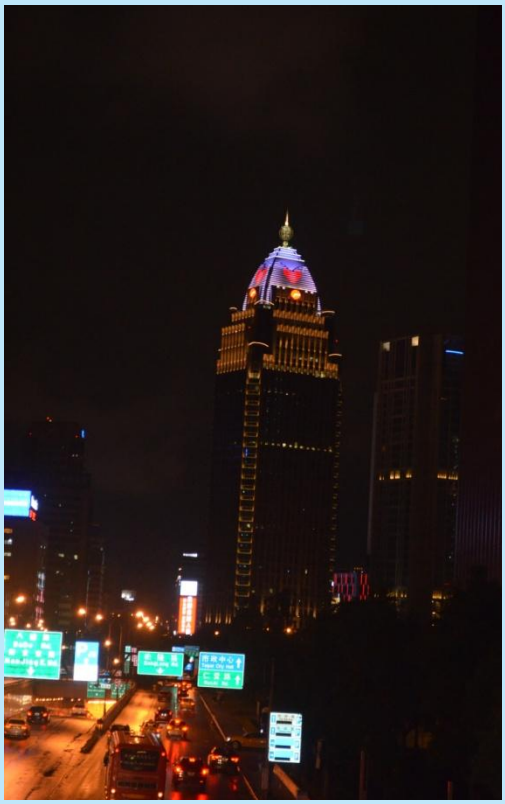

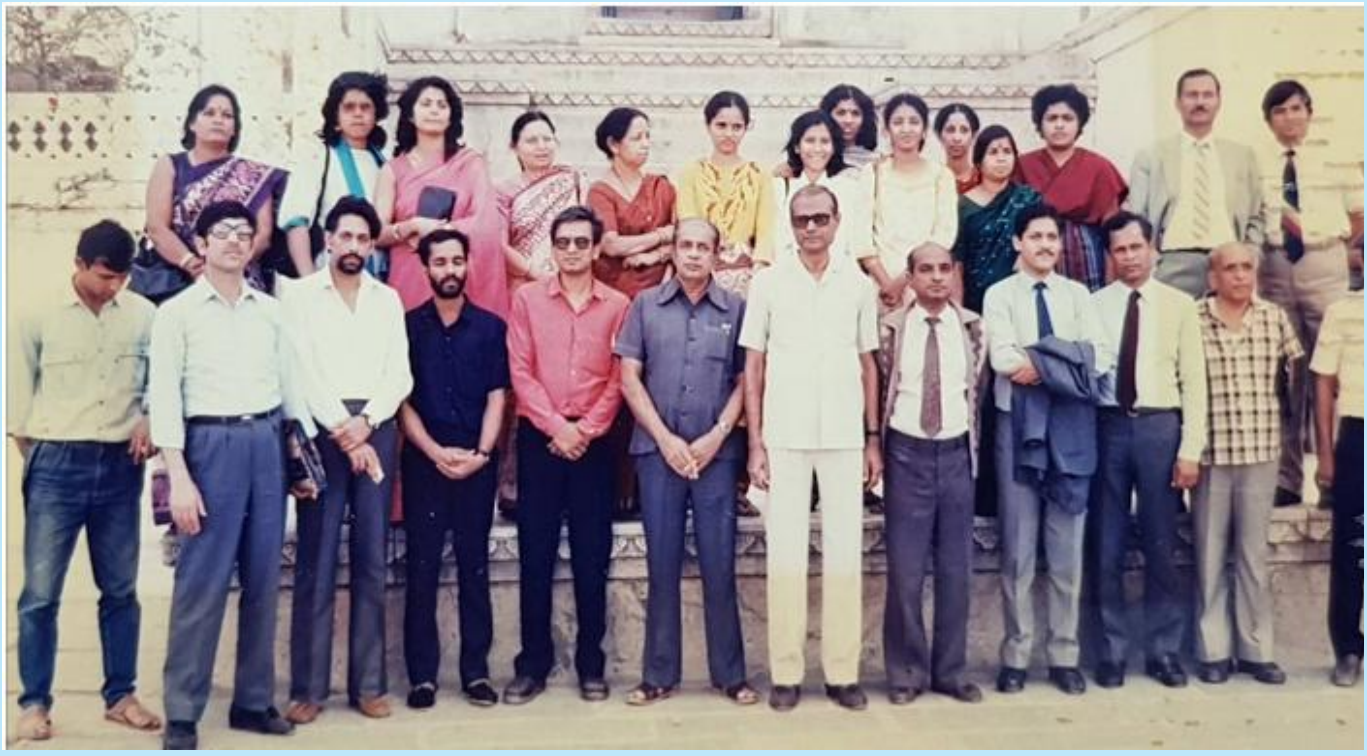

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