

ISSN 1810-1828
Medicine Today 2014, Volum 26 Number 01

MEDICINE today

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Volume 25, July 2013

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Production Editing: Medical Services Department Biopharma Ltd.
e-mail: medicinetoday@biopharmabd.com

Published by: Dr. Lokuat Ullah

Printed at: Helpline Resources
46/1, Purana Paltan
Dhaka-1000

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Subscription information:

Journal of Medicine Today ISSN 1810-1828 published by the Dr. Md. Lokial Ullah, Executive Director, BIOPHARMA LTD. two times a year in January and July.

Address of correspondence:

Manuscripts and other communication for the editors should be addressed to Medicine Today, **Medical Services Department**, Biopharma Ltd. 7/16, Block-B, Lalmatia, Dhaka-1207.
e-mail: medicinetoday@biopharmabd.com
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Drug Addiction- A Silent Killer for Society

Minar AW¹

Drug addiction is widely considered as a pathological state. The disorder of addiction involves the progression of acute drug use to the development of drug seeking behavior, the vulnerability to relapse, and the decreased, slowed ability to respond to naturally rewarding stimuli¹.

Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial and environmental factors influencing the development and manifestations. Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing the blood level of drug and or administration of an antagonist².

Drug addiction is an epidemiological problem worldwide including Bangladesh. National survey shows that 0.16% population are related with substance use disorder among which adolescent group are more vulnerable. Epidemiological studies indicate that experimentation with addictive drugs and onset of addictive disorders is primarily concentrated in adolescence and young adulthood. An exploration of developmental changes in neurocircuitry involved in impulse control has significant implications for understanding adolescent behavior, addiction vulnerability, and the prevention of addiction in adolescent and adulthood.

Substance use disorders are a leading cause of medical morbidity, mortality and health expenditure in the United States and other developed countries. Regional availability of substance and social trends influence the prevalence of specific substance abuse disorders. Three major observations suggest that the Developmental periods of adolescent and adulthood are primary correlates of substance use and substance use disorders, operating across cultural trends and substances. First, adolescent and young adults generally exhibit higher rates of experimental use and substance use disorders than older adults, as indicated by studies of the general population spanning the last two decades and with the use of alternate diagnostic criteria.

Second, addictive disorders identified in adults most commonly have onset in adolescent or young adulthood . For example , most adult U.S smokers start smoking before 18 and the onset of daily smoking is uncommon after age 25. Over 40% of adult alcoholic experience alcoholism related symptoms begin between age 15 and 19, and 80% of all cases of all alcoholism begin before age 30. The age of initiation of illicit drug use in adults with substance use disorders is 16 years , with 50% of cases beginning between age 15 and 18 and rare initiation after age 20.

Third, earlier onset of substance use predicts greater addiction severity and morbidity including use of and substance use disorders associated with multiple substances. Two key variables in the genesis of addictive disorders are the 1) degree / amount of drug intake and 2) the inherent vulnerability to addiction given a fixed amount of drug intake. Understanding whether one or both these factors are greater in adolescence is important in explaining the developmental onset of substance use disorders . Although cultural , peer, and family influences contribute to drug availability and substance experimentation, several lines of evidence suggest that sociocultural aspects particular to adolescent life alone don't fully account for greater drug intake. Although marketing and the availability of legal drugs (alcohol and nicotine) are pervasive across the groups in American society and are legally sanctioned only for adults, the onset of substance use disorders associated with these drugs is concentrated in adolescent and young adulthood and does not increase in a cumulative manner with increase age.

Genetic and neurobiological factors within individuals are thought to Lower the threshold of drug exposure required for " tripping the switch" from experimental to addictive drug use. Growing clinical evidence suggests that adolescence represents a period of heightened biological vulnerability to the addictive properties of illegal and legally sanctioned substance. For instance, adolescents demonstrate a more precipitous progression of illicit drug use than adults. Despite smoking fewer cigarettes than adults, adolescent show higher rates of dependence at similar level of use, although rates of alcohol use are similar throughout adolescence and adulthood, rates of abuse / dependence vary inversely with age. It is shown that basic and clinical evidence for adolescent neurodevelopment as a critical period of addiction vulnerability. Behaviors seemingly characterized by impulsivity and suboptimal decision making are described as normative traits of adolescence corresponding to the development of motivational circuitry involve in the pathophysiology of addiction.

The prevalence of substance use disorders is elevated in adults with Schizophrenia, major affective disorders, antisocial and borderline personality disorders and pathological gambling. Adolescent with antecedent or fully expressed versions of these disorders are also more likely to have substance use disorders. Associations of these mental illnesses and adolescence with substance use disorders suggests that common brain mechanisms may underlie vulnerability to substance use disorders in these contexts.

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Psychiatric disorders commonly identified with disturbances in reward motivation and substance use disorder co morbidity is associated with impulsivity. Understanding the relationship between impulsivity and substance use disorders may prove important to understanding the pathogenesis of substance use disorders and their greater prevalence in specific clinical contexts, including adolescence. Individuals with poor impulse control show a thematic tendency to engage in behaviors characterized by long - term disadvantageous outcomes.

When examining the biological basis of drug addiction, one must first understand the pathways in which drugs act and how drugs can alter those pathways. The reward circuit , also referred to as the Mesolimbic system, is characterized by the interaction of the several areas of the brain.

The ventral tegmental area (VTA) consists of dopamine rigid neurons which respond to glutamate. The VTA supports learning and sensitization development and release dopamine (DA) into the forebrain³. These neurons also project and release DA into the nucleus accumbens, through the Mesolimbic pathway. Vertically all drugs causing drug addiction increase the dopamine release in the Mesolimbic pathway⁴.

The nucleus accumbens(NAcc) consists mainly of medium-spiny projection neurons(MSNs) which are GABA neurons. The NAcc is associated with acquiring and eliciting conditioned behaviors and involved in the increased sensitivity to drugs as addiction progresses³.

The prefrontal cortex, more specifically the anterior cingulate and orbitofrontal Cortices , is important for the integration of information which contribute to whether a behavior will be elicited. It appears to be the area in which motivation originates and the salience of stimuli are determined⁵.

The baso lateral amygdala projects into the NAcc and is thought to be important for motivation as well⁵. More evidence is pointing towards the role of the hippocampus in drug addiction because of its importance in learning and memory⁶. So, cortical-striatal- thalamic -cortical loops are described as parallel because specific sub regions of the prefrontal cortex project to specific compartments within the striatum, which in turn maintain some degree of segregation in projection to the thalamus and back to the cortex. Firing pattern in both the nucleus accumbens and prefrontal cortex are influenced by glutamatergic inputs from the hippocampus and amygdala, suggesting the abnormalities in this distal structures may produce both mental illness and motivational disorders.

Several explanations have been presented to explain addiction. These divide, more or less, into the models which stress biological or genetic causes for addiction, and those which stress social or purely psychological causes. Of course there are also many models which attempt to see addiction as both a physiological and psycho- social phenomenon.

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Platelet Hyper-Aggregation and Abnormalities of Coagulation Factors in Young Diabetic Patients

Huque M¹, Ahmed T², Ali L³, Zinnat R⁴, Mahtab H⁵, Bhuiyan MM⁶

Abstract

Diabetic vascular disease is conveniently divided into two main categories: microvascular diseases and macrovascular diseases. The changes involving the smallest blood vessels - the capillary and pre-capillary arterioles - are microvascular changes. The cross sectional case-control study was done on forty young diabetic patients for their platelet aggregation response to ADP, plasma fibrinogen and vWF in relation to the age and BMI matched 10 nondiabetic control subjects (Age in years : 23.7 ± 2.26 in control vs 24.33 ± 3.29 in subjects, and BMI in kg/m². The lipid profile, C-peptide, C-peptide: glucose and other anthropometric measurements of the diabetic and control subjects were also measured to find out any possible correlation. The platelet aggregation with ADP in diabetics was found to be significantly higher (in diabetics 76.56 ± 16.92 percent compared to controls 62.90 ± 12.35 percents; ($P < 0.27$). Plasma fibrinogen and plasma von Willebrand factors were found to be significantly higher in young diabetics compared to the non-diabetic counterparts (Plasma fibrinogen in mg/l; 1075.90 ± 455.16 in control vs 1569.15 ± 731.42 in diabetic, $P < 0.048$; plasma vWF in iu/ml; 1.372 ± 0.340 in control vs 1.884 ± 0.51 in diabetic, $P < 0.001$). Fasting plasma glucose was higher and C-peptide - glucose ratio lower in diabetic subjects compared to the controls (Fasting plasma glucose in mmol/l; 3.48 ± 0.38 in control vs 16.02 ± 8.58 in diabetic; C-peptide-glucose ratio 0.426 ± 0.133 in controls vs 0.116 ± 0.105 in diabetics, $P < .001$). Thus hyperglycemia, endothelial dysfunction, elevated vWF and insulin resistance were supposed to be interlinked.

Introduction

Vascular complications are common in diabetes mellitus and are leading causes of morbidity and mortality due to the disease. Platelet hyperaggregation and coagulation factor abnormalities have been implicated in the increased prevalence of vascular complications. However, their precise role is uncertain and it is also not known whether they are primary or secondary in nature. Moreover, the precise role of hyperglycemia in the development of these abnormalities have remained similarly uncertain. To help in understanding the pathogenesis of platelet hyperaggregation and coagulation factor abnormalities in diabetes mellitus and to explore the role of hyperglycemia, this study was done on a group of young, non-obese, normotensive and untreated Bangladeshi diabetic subjects. This has enabled to explore the role of hyperglycemia in the absence of the confounding variables and also to investigate the interrelationship among the presumed risk factors leading to vasculopathy.

Diabetic vascular disease is conveniently divided into two main categories: microvascular diseases and macrovascular diseases. The changes involving the smallest blood vessels - the capillary and pre-capillary arterioles - are microvascular changes. Sequential features of these changes are: (a) pre-capillary vasodilatation and hyperfiltration of fluid, (b) increased basement membrane formation and (c) breakdown of normal chargebarrier causing increased transcapillary escape of albumin. In advanced cases, loss of vessel caliber and vascular occlusion ensues¹.

Microvascular changes involve the retina, kidneys, vasa nervosum and heart. Pathologically, microvascular involvement of glomeruli leads to diabetic nephropathy and retinal involvement gives retinopathy. Small vessel diseases also involve the heart and cardiomegaly with heart failure has been described with patent coronary arteries. It has long been postulated that microvascular lesions play a role in the production of macrovascular diseases also. But it needs further study to confirm the speculation².

The hall mark of macrovascular complications is atherosclerosis both in nondiabetics and diabetics with the same sequence of events of pathogenesis as (a) endothelial injury; (b) platelet adhesion and aggregation with the release of mediators (c) smooth muscle proliferation and migration into sub-endothelium at the area of damage; (d) accumulation of extracellular matrix, lipids and lipoproteins; and (e) thrombosis, the process is reversible with counter-regulatory events and accelerated by impaired host response to any of the above events³.

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But in diabetics these events appear earlier and are more extensive and associated with higher mortality and morbidity.

A reason for increased platelet aggregability in platelet rich plasma from diabetic subjects is platelet-plasma interaction. A-"platelet aggregation enhancing factor" has been described to be present in many diabetic patients. This plasma factor would interact with platelets to make them more sensitive to ADP- induced aggregation. Plasma factor activity was greatest in patients with retinopathy and nephropathy⁴. However the source of PAEF activity has not been fully identified. Some of the logical candidates would include vWF, fibrinogen, immune complexes, free fatty acids, other lipids and lipoproteins. Again there are controversies about the role of fibrinogen and vWF (coagulation factors) in inducing vascular complications in diabetics. Some studies show convincing evidences and some are inconclusive or against the proportion. It is not clear whether the prognostic value of vWF is related to its specific functions of enhancement of platelet adhesion and factor VIII availability, or whether it is simply an indication of endothelial injury and dysfunction. But this endothelial dysfunction and injury may be responsible for increased risk of nephropathy and cardiovascular disease. Elevated vWF may also precede initial neuropathy-both autonomic and peripheral. vWF factor may also predict alterations in nerve function independent of glycemic control. But retinopathy was not found to be related with alteration in vWF level in type-1 diabetic subjects⁵.

Materials and Methods

The cross sectional analytical study was done on 50 patients in Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic disorders (BIRDEM). Forty (40) subjects were newly diagnosed young (age range 24±3, 18 male 22 female) diabetes, consecutively attending the Out-patients Department of BIRDEM, Dhaka.

Control subjects were selected from friends of the patients without any family history of diabetes up to second generation (n=10) within 5 years age band. Control subjects were matched for BMI, urban/rural setting and socio-economic status with their diabetic counterparts.

Exclusion criteria

1. Diabetic subjects suffering from chronic illness, nondiabetic renal disease and pregnancy were excluded from the study.
2. Diabetic subjects with ketosis and history of antidiabetic treatment were also excluded.
3. Both the diabetic subjects and healthy controls with parental history of essential hypertension were also excluded.

Detailed sociodemographic data, Anthropometric measurements, family history of diabetes, medical history, physical and clinical examinations were done on the very first day of visit. Platelet aggregation was measured by Optical Aggregation Test and plasma Fibrinogen and von Willebrand Factor (vWF : Ag) was measured by radio-immuno-diffusion method.

Results

Fifty subjects were studied in this project. Forty were young diabetic subjects (under 30 years of age) and ten were control. The mean ($\pm$ SD) age of the diabetic subjects was 24.33 ± 3.29 years and in control subjects the mean age was 23.70 ± 2.26 years. There was no significant difference in age between control and the diabetics.

The BMI of the two groups was also matched. (BMI in kg/m² 20.68 ± 5.78 in diabetics and 20.52 ± 2.05 in controls).

The groups had similar systolic blood pressure (blood pressure in mm. of Hg: 107.5 ± 8.58) in controls and 108.13 ± 13.7 in diabetics) but significant difference was observed in diastolic blood pressure (blood pressure in mm of Hg : 63.50 ± 4.74 in control vs 71.38 ± 9.67 in diabetic; $P < 0.001$) (Table-I).

Their mid-arm circumference and sub-scapular-triceps ratio were also matched.

Results are expressed as mean $\pm$ SD. Unpaired student's t-test was performed.

Table - I: Anthropometric features of different groups of study subjects.

Groups	Age (years)	BMI (kg/m ²)	MAC (cm)	STR	WHR	sBP (mmHg)	dBP (mmHg)
Control (n= 10)	23.70±2.26	20.52±2.05	22.80±2.40	1.46±0.59	0.81±5.97	107.50±8.58	63.50±4.74
Diabetic (n=40)	24.33±3.29	20.68±5.78	22.81±4.90	1.80±0.48	0.88±7.50	108.13±13.7	71.38±9.67

N = number of subjects, BMI = Body mass index, MAC = Mid arm circumference, STR = Subscapular triceps ratio

WHR = Waist hip ratio, sBP = Systolic blood pressure, dBP = Diastolic blood pressure

Both fasting plasma glucose and C-peptide : glucose ratio were highly significant in diabetic subjects compared to the control subjects.

Fasting plasma glucose in mmol/l; 3.48 ± 0.38 in control vs 16.02 ± 8.58 , $P < 0.00$. C-peptide : glucose ratio in controls 0.426 ± 0.133 , vs 0.116 ± 0.105 , in young diabetics. But no significant difference was found in C-peptide levels in control and diabetic groups (Table-II).

Results are expressed as mean $\pm$ SD. Unpaired student's t-test was performed.

Table- II: Glycemic status of different groups of study subjects.

Groups	F-glucose (mmol/l)	C-peptide (ng/ml)	C-peptide : Glucose
Control (n= 10)	3.48 $\pm$ 0.38	1.44 $\pm$ 0.33	0.426 $\pm$ 0.133
Young diabetics (n=40)	16.02 $\pm$ 8.58	130. $\pm$ 0.84	0.116 $\pm$ 0.105
t/p value	9.21/0.00	0.53/0.59	6.83/0.00

N = number of subjects, F = Glucose; fasting glucose, C-peptide = Connecting peptide

Platelet aggregation by ADP in controls was found to be 62.90 ± 12.35 percent compared to the diabetics 76.56 ± 16.92 percent. Data indicated that there was increase in percent of aggregation induced by ADP in diabetics and found to be significant ($P < 0.027$) (Table-III).

But no difference was observed in platelet count between two groups.

Table- III: Platelet count, platelet aggregation, plasma fibrinogen and von Willebrand factor status of the study subjects.

Groups	Platelet count /mm ³	Platelet aggregation by ADP %	Plasma fibrinogen mg/l	Plasma vWF iu/ml
Control (n= 10)	207300 $\pm$ 44236	62.90 $\pm$ 12.35	1075.90 $\pm$ 455.16	1.372 $\pm$ 0.340
Diabetic (n=40)	221650 $\pm$ 61555	76.56 $\pm$ 16.92	1569.15 $\pm$ 731.42	1.884 $\pm$ 0.51
t/p value	0.691/0.493	2.283/0.027	2.027/0.048	3.818 / 0.001

Plasma fibrinogen and plasma von Willebrand factors were found to be significant in young diabetics compared to the non-diabetic counterparts. Specially plasma vWF was found to be highly significant.

Plasma fibrinogen in mg/l; 1075.90 $\pm$ 455.16 in control vs 1569.15 $\pm$ 731.42 in diabetic, $P < 0.048$). Plasma vWF in iu/ml; 1.372 $\pm$ 0.340 in control vs 1.884 $\pm$ 0.51 in diabetic, $P < 0.001$ (Table-IV).

Table-IV: Pearson correlation coefficient between von Willebrand factor and anthropometric

Groups	BMI		WHR		STR		MAC	
	r	p	r	p	r	p	r	p
Diabetic (n=40)	0.006	0.970	-0.058	0.722	0.037	0.821	0.066	0.684

BMI = Body mass index, WHR = Waist hip ratio, STR = Subscapular triceps ratio, MAC = Mid arm circumference

r = Pearson correlation coefficient, P = Significant value for 'r', N = number of subjects

Table- V: Pearson correlation coefficient between plasma fibrinogen and anthropometric status

Groups	BMI		WHR		STR		MAC	
	r	p	r	p	r	p	r	p
Diabetic (n=40)	0.295	.065	-0.105	0.518	0.006	0.971	0.237	0.140

Statistical analysis were performed by Bivariant correlation of pearson coefficient

Discussion

There is now overwhelming evidence that a procoagulant state exists in diabetic subjects, but there is a great deal of controversy regarding the primary or secondary nature of this state. The question is important to be solved because it addresses the basic question about the causal relation of coagulation factors in the genesis of macro and microvascular diseases in diabetes mellitus. In turn, this have important implication in the management of diabetes mellitus and its complications.

The role of platelets in arterial in arterial thrombosis is similar to their role in hemostasis. In the hemostatic. Reaction, platelets adhere to the damaged vessel wall and aggregate to each other, releasing ADP and initiating the chain of events leading to the formation of a white thrombus⁶

Substantial endothelial damage and contact of platelets with collagen fibers, basement membrane and microfibrils of the vessel wall are required to initiate arterial thrombosis. There is a postulation that platelet activation may lead to the release of mediators which may secondarily influence the development of coagulation factor abnormalities⁷.

The present findings do not seem to support the view since there was no correlation between platelet aggregation and any of the coagulation factors. Also, no correlation was observed in between any of the two coagulation factors suggesting that the change in the levels of these factors may reflect primary changes which are still not clearly understood. A genetic predisposition which may coexist with the diabetic condition may be a possibility. However, further detail studies on the metabolic changes in relation to endothelial function, may generate valuable results for solving this issue.

Endothelial damage or dysfunction causing angiopathy is the main cause of morbidity and mortality in diabetes mellitus. Glycemic control seems to be insufficient to normalize vWF but other specific treatments required. vWF appears to be a predictive marker of diabetic nephropathy and neuropathy which suggests that endothelial dysfunction precede the onset of diabetic macroangiopathy. At present, it is not known, whether high vWF levels are inherent to this physiopathology of diabetes, nor whether diabetes induces endothelial dysfunction through other ways⁸.

Hyper fibrinogenemia has emerged as an independent predictive risk factor for CHD. Indeed hyperfibrinogenemia now appears to challenge the rank power of hypercholesterolemia as a predictive and independent risk factor. These varied observations provide an important link between altered haemostasis, thrombosis and clinical CHD. Intervention strategies are targeted to the areas of thromboresistance also⁹.

From the present study, it was observed that in young diabetics, platelet hyperaggregation and coagulation factor abnormalities appear quite early and seem to play important role in the natural history of vasculopathy in diabetes mellitus. Diabetic condition (as evidenced by hyperglycemia), by itself, may create platelet hyperaggregation and coagulation factor abnormalities. However, there seems to be no straightforward relationship between those abnormalities and the degree of hyperglycemia. Factors other than glucose may be involved in the genesis of the above abnormalities as primary or secondary events. Platelet hyperaggregation, hyperfibrinogenemia and increased vWF do not influence each other in a direct manner.

More detailed studies on genetic factors and endothelial metabolic abnormalities, with long-term follow-up, may clarify the primary or secondary nature of procoagulant abnormalities in diabetes mellitus.

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Levonorgestrel Releasing Intrauterine System in the Treatment of Dysfunctional Uterine Bleeding

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Abstract

This study was designed to determine progress of women presenting with dysfunctional uterine bleeding (i.e decrease in amount and duration of bleeding in days) due to a cause amenable to treatment. To evaluate improvement in Haemoglobin level (Hb gm%) in patients during treatment.

The study was conducted in the Department of Obstetrics & Gynaecology, Chittagong Medical College Hospital, Chittagong, Bangladesh from August 2008 to July 2010. Thirty six patients with Dysfunctional Uterine Bleeding (DUB) in 30-45 years age group with Body Mass Index (BMI) Of 18-30 during treatment period were included in the study. They were counselled, investigated and had Levonogestrel Intrauterine device inserted. Outcome was measured by Hb improvement and decrease in blood loss both in amount and duration. Record was kept and follow up was done.

Ninety percent of the patients were relieved from menorrhagia and one hundred percent improvement was seen in cases with polymenorrhagia. 50% patients had an Hb of >11.1gm% after 3 months of use.

Levonogestrel intrauterine system or LNG-IUS is a safe and effective device for the treatment of DUB patients and it is an alternative to hysterectomy.

Key Words: Uterine bleeding, dysfunctional uterine bleeding

Introduction

Abnormal menstrual bleeding is one of the most common complaints that we come across everyday and it is a serious health risk due to anaemia and general disability. "Dysfunctional uterine bleeding" is the term applied to the abnormal bleeding patterns that occur in women secondary to anovulation or oligo-ovulation and is often referred to as anovulatory bleeding and in the absence of organic cause. It may be menorrhagia, metrorrhagia, polymenorrhagia and polymenorrhea. An estimated one third of all outpatient gynecological visits are for abnormal uterine bleeding¹.

The management options available are prostaglandin synthetase inhibitors, antifibrinolytics and progestins, combined estrogen and progestins, danazol, GnRH agonists and antagonists. Also, conservative surgical techniques like Endometrial resection, thermal balloon ablation, laser ablation are available. Of the 600,000 hysterectomies performed each year in the US, 20% are for DUB¹. Among the management options available for anovulatory abnormal uterine bleeding cyclic progestins offer a therapeutic option. In ovulatory cycles cyclic progestins from day 5-25 of the cycle were significantly less effective at reducing menstrual blood loss than progesterone releasing-IUS as continuous progestins lead to endometrial atrophy¹.

Levonogestrel intrauterine system or LNG-IUS is used for the treatment of abnormal bleeding and women prefer it over cyclic therapy. Mirena is shown to decrease the amount of bleeding by 79-94%². It also decreases the operative treatments like hysterectomy³. 64-82% patients on waiting list decline hysterectomy⁴. The objectives of this study were to determine the women diagnosed with DUB treated with Mirena that decrease the amount and duration of bleeding. Also to evaluate correction of anaemia in the form of improvement in Hb gm% during treatment.

Materials and Methods

This study was conducted in the Department of Obstetrics & Gynaecology, Chittagong Medical College Hospital, Chittagong from August 2008 - July 2010. It was a prospective interventional study. Women diagnosed with DUB accepting contraceptives during treatment period in the age group of 30-45 years with a BMI of 18-30 were included in the study. The exclusion criteria was known or suspected pregnancy, current or recurrent PID, Postpartum endometritis, fibroid, adenomyosis, Cervical dysplasia, undiagnosed abnormal vaginal bleeding, congenital abnormality of uterus, acute liver disease and previous history of deep venous thrombosis. Patients were counseled, investigated and informed consent taken. LNG-IUS was inserted as per instructions. A record was kept of followup visits at 1, 3, 6 and 9 months and 1 year and 2 years after insertion. Outcome was measured in terms of patient satisfaction, improvement in Hb% and decreased blood loss (duration and bleeding) and the results were compiled according to the above mentioned outcome measures.

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Results

Table I shows the age distribution in patients selected for LNG-IUS use. Maximum patients i.e 44.45% were in the age range of 35-39 years. Table II shows change in Hb% with treatment. The maximum number of patients had an overall reduction of days of bleeding from an average 9 to 4.5-5 days. Table III shows the improvement of symptoms. The early problems faced by patients with LNG-IUS insertion were as follows. Ten (25%) patients had backache which eased with simple analgesics. Eight patients had short term spotting and irregular bleeding. Two patients had some infection and one patient expelled LNG-IUS which was reinserted. 55.55% patients who had been advised hysterectomy decided to take LNG-IUS and were satisfied with the device.

Table I: Age distribution (n = 36)

Age Range	Frequency
30-34 Years	8 (22.22%)
35-39 Years	16 (44.45%)
40-44 Years	12 (33.33%)

Mean age was 37.55 years

Standard deviation was ± 4.03

Table II: Change in Hb% with Mirena use (n=36)

Hb gm%	No of patients at insertion of LNG-IUS	No of patients 3 months after insertion of LNG-IUS
<9 gm%	14 (38.88%)	0%
9 – 10 gm%	16 (44.46%)	6 (16.66%)
10.1 – 11 gm%	6 (16.66%)	12 (33.34%)
>11.1 gm%	0%	18 (50%)

Before LNG-IUS insertion

Mean hemoglobin level was 9.3 gm%

Standard deviation was ± 0.86

After LNG-IUS insertion

Mean hemoglobin level was 11.1 gm%

Standard deviation was ± 1.92

Table III: Patients reporting symptom relief (n=36)

Group	Symptoms	No of patients reporting symptoms	No of patients relieved
Menorrhagia	Menorrhagia/ Dysmenorrhea	20	18 (90.00%)
Irregular Cycle	1. Polymenorrhea	9	9 (100%)
	2. Metrorrhagia	3	3 (100%)
	3. Menometrorrhagia	1	1 (100%)
	4. Polymenorrhea + Menorrhagia	3	2 (66.66%)

Discussion

LNG-IUS is used for the treatment of abnormal bleeding and women are more satisfied and willing to continue with LNG-IUS compared to cyclic therapy. LNG-IUS has shown to decrease the amount of bleeding over time by 79-94%. Twenty (55.55%) out of 36 patients who had been advised hysterectomy in our study decided against it. This is comparable to other studies in which 64-82% patients who were on the waiting list declined hysterectomy^{5,6,7}. In a study published in 2009 the 5 year intervention free percentage of patients with LNG-IUS was 70.6% (SD + 3.3%)⁸. Another study reports that in improperly assessed and selected obese, premenopausal women with DUB at high risk for traditional therapies, the LNG-IUS was an effective treatment in 70% of patients^{9,10}. In our study the overall reduction of days of bleeding was from an average of 9 days to 4.5-5 days which is comparable to other studies^{11,12,13}.

In case of dysfunctional uterine bleeding, the use of medical treatment should be considered as the first line treatment. Progestogens are often used in this condition and LNG-IUS is very effective^{14,15}. After 3 months of insertion of LNG-IUS a marked decrease was seen in anaemia. An Hb of < 9 gm% was seen in 38.88% patients before LNG-IUS insertion and after 3 months of LNG-IUS not a single patient had an Hb < 9gm%. Our study confirms the efficacy of levonorgestrel releasing intra-uterine system in the control and reduction of menstrual blood loss in patients with dysfunctional uterine bleeding. The LNG-IUS as an alternative treatment to hysterectomy in case of DUB patients and in this patients thus leading to a reduction in morbidity associated with surgery, cost of surgery, stay in hospital and also workload on the surgeons and hospital staff.

We conclude that LNG-IUS is a safe and effective device to be offered as treatment to patients with DUB. It is an alternative to hysterectomy and we strongly recommend its use. The limitation that we found was its high cost otherwise a larger number of patients could have been included.

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Study of Thyroid Hormonal Status in Preeclamptic Patients

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Abstract

The physiological changes in the thyroid gland during pregnancy were well understood. Serum TSH levels were significantly increased without changes in free T₃ and T₄ in preeclamptic patient compared to normal pregnancy. This study tried to find out a possible relationship between preeclampsia and thyroid profile.

The present study determines thyroid hormonal levels in cases of preeclampsia in the third trimester of pregnancy. TSH level were significantly higher in preeclamptic group as compared to control.

A prospective case control study was conducted in the Department of Obstetrics and Gynecology, Chittagong Medical College Hospital, Chittagong.

Thyroid hormone, namely Triiodothyronine (Free T₃), Thyroxine (Free T₄) and Thyroid Stimulating Hormone (TSH) were evaluated by radioimmunoassay. In this case control study pregnant women with preeclampsia were recruited after the diagnosis were made and compared with equal number of healthy normotensive pregnant women in third trimester.

The data were analyzed using unpaired 't' test and chi-square test. When P value were <0.05, the result were accepted as significant.

Increase TSH level were associated with a risk for occurrence of preeclampsia.

Key Words: Hypothyroidism, preeclampsia, pregnancy and thyroid hormones

Introduction

Hypertensive disease in pregnancy is a major cause of maternal and fetal morbidity and mortality¹. PE adversely affects the maternal and fetal outcome due to its wide spread multi organ involvement. PE is a complication in approximately 5% of all pregnancies¹.

The incidence in primigravida is about 10% and in multigravida 5%. PE is one of the most common causes of perinatal morbidity and mortality resulting in an estimated 35 ~ 300 deaths per 1000 births depending on neonatal support¹.

PE usually occurs in women at both extremes of reproductive age however the risk of PE is greatest in women younger than 20 years¹. PE is more prevalent in developing countries like Bangladesh where poverty, malnutrition, micronutrient deficiencies, early marriage, early child birth and lack of antenatal care are more common.

In Bangladesh the incidence of PE is very high. It is about 10 ~ 15% of all deliveries and it remains one of the commonest (about 16%) cause of maternal death being in the third position of all MMR².

So preeclampsia is a matter of great concern for the obstetrician as well as pregnant women and for the nation. The exact cause of preeclampsia has not been identified. Numerous theories of potential causes exist including genetic, dietary, vascular and auto immune factors³. The causes of PE remains unknown however placental dysfunction many initiate the systematic vasospasm, ischemia and thrombosis that eventually damages maternal organs.

The mechanism of hypothyroidism in preeclamptic women has not been identified but the changes in thyroid function during pregnancy are accounted for high circulating oestrogen⁴. There are different views about the mechanism and clinical significance of low concentrations of thyroid hormones in PE, which are attributed to decrease plasma protein concentrations and high levels of endothelin, a potent vasoconstrictor produced by vascular endothelium after a vascular injury^{5,6}.

There is a relationship between PE and thyroid profile. Serum TSH level significantly increased without concomitant changes in T₃ and T₄ in PE compared to normal pregnancy⁷. Thus TSH was found to be strong associating factor for the occurrence of PE.

Materials and Methods

This was a descriptive cross sectional study. The study period was from January 2005 to December 2005 was conducted at in-patient department of Obstetrics &

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consecutively admitted with the diagnosis of preeclampsia in the third trimester were recruited for the study.

The inclusion criteria were: (a) Preeclamptic patients in the third trimester of pregnancy, (b) Healthy pregnant women in the third trimester of pregnancy.

The exclusion criteria for both the groups were: (a) The patient with pregnancy induced hypertension (PIH) without proteinuria, (b) the pregnant women with previous history of thyroid diseases or metabolic disorders, maternal history of taking antithyroid drugs, (c) History of thyroid surgery or treatment with RAI, (d) Pregnancy with chronic renal disease, (e) History of multiple pregnancies, (f) Pregnancy with chronic hypertension, (g) Chronic liver disease and (h) Medication with diuretics, steroids and anti-HTN drugs.

10 ml venous blood sample was taken from the cubital vein of (i) preeclamptic women, after the diagnosis was made but before the initiation of the antihypertensive treatment, and before the delivery and (ii) each control subject as mentioned above. All samples were sent to the laboratory with different code numbers. Sera was separated and stored at -20°C until assayed. Free T_3 (triiodothyronine), free T_4 (thyroxine) and TSH (thyroid-stimulating hormone) were measured using radioimmunoassay. All women were followed up through their antenatal, intrapartum and postpartum period. They were especially observed for the development of the symptoms and signs of hypothyroidism. Data were statistically analyzed by computer with SPSS (Version 11.5). Mean values were calculated to see the central tendency, standard deviation, standard error were calculated to assess the dispersion of the data and the Student's 't' test, Chi-square test were performed to detect statistical significance of the observations. A probability value (p - value) of < 0.05 was considered significant with 95% CI.

Results

A total 104 pregnant women were included in this study. Among them 52 women with the diagnosis of preeclampsia selected as Case and 52 were normal pregnant women as control.

Age, parity and gestational age of participant group:

The mean ($\pm$ SD) age of the study group and control group were 26.15 ± 4.17 years and 26.19 ± 4.20 years respectively and there was no statistically significant difference between the two groups ($p > 0.05$).

The mean ($\pm$ SD) parity of the study group and control group were 1.28 ± 0.90 years and 1.30 ± 0.88 years respectively and there was no statistically significant difference between the two groups ($p > 0.05$).

The mean ($\pm$ SD) gestational age at the time of taking the blood sample for thyroid hormonal level was 34.30 ± 2.92 weeks in the study group and 35.10 ± 2.82 weeks was in the control group. The difference between the two groups was not statistically significant ($p = 0.55$). The results are shown in Table-I.

Table -I: Age, parity and gestational age of participant groups

Parameters	Control	Case	t- value	p- value	dF
Age in years (Mean $\pm$ SD)	26.19 $\pm$ 4.20	26.15 $\pm$ 4.17	0.05	0.9618	102
Parity (Mean $\pm$ SD)	1.30 $\pm$ 0.88	1.28 $\pm$ 0.90	0.044	0.0670	102
Gestational age in weeks (Mean $\pm$ SD)	35.10 $\pm$ 2.82	34.30 $\pm$ 2.92	0.35	0.5500	102

Thyroid function tests

The mean ($\pm$ SD) TSH of the study group and control group were 4.14 ± 2.24 mIU/L and 2.75 ± 1.73 mIU/L respectively and there was highly significant difference between the two groups ($p = 0.0007$).

The mean ($\pm$ SD) T_3 of the study group and control group were 1.95 ± 0.64 nmol/L and 1.98 ± 0.57 nmol/L respectively and there was no significant difference between the two groups ($p > 0.05$).

The mean ($\pm$ SD) T_4 of 128.38 ± 33.43 nmol/L was in the study group and 126.37 ± 34.70

nmol/L was in the control group. The difference between the two groups was not statistically significant ($p > 0.05$). The results are shown in Table-II.

Table -II: Thyroid function tests of participants groups

Parameters	Control	Case	t- value	p- value	dF
TSH (mIU/L) (Mean $\pm$ SD)	2.75 $\pm$ 1.73	4.14 $\pm$ 2.24	3.51	0.0007	102
T_3 (nmol/L) (Mean $\pm$ SD)	1.98 $\pm$ 0.57	1.95 $\pm$ 0.64	0.267	0.7900	102
T_4 (nmol/L) (Mean $\pm$ SD)	126.37 $\pm$ 34.70	128.38 $\pm$ 33.43	0.30	0.7664	102

TSH levels of both case and control groups

Out of 52 pregnant women in study group, 21 (40.40%) had higher TSH titers (> 4.8 mIU/L) and 52 pregnant women in control group, 9 (17.30%) had higher TSH titers (> 4.8 mIU/L). Twenty one (70.00%) of the 30 pregnant women with abnormal TSH titers, had the diagnosis of preeclampsia whereas 31 (41.90%) of the 74 pregnant women with normal TSH titers, had preeclampsia in the third trimester. This difference between the two groups was statistically significant ($p = 0.009$), degrees of freedom was 1. Odds ratio indicates that preeclampsia group have chance of higher TSH (> 4.8 mIU/L) by 3.24 times. The results are shown in Table-III.

Table -III: Distribution of normal and increased TSH levels in both preeclamptic and control groups

Group	TSH Group		Total	Odds ratio (95% confidence interval)	X ² -value	p-value	dF
	TSH < 4.8 mIU/L	TSH > 4.8 mIU/L					
Control	43 82.70%	9 17.30%	52	1.00	6.75	0.009	1
Case	31 59.60%	21 40.40%	52	3.24 (2.18-10.54)			
Total	74	30	104				

Discussion

This study was conducted in the Obstetrics and Gynecology Department of CMCH, Chittagong with the intention to determine the thyroid hormonal levels in case of 52 preeclamptic patients and 52 matched controls in the third trimester.

In this study the mean ($\pm$ SD) age of the study group and control group were 26.15 ± 4.17 and 26.19 ± 4.20 years respectively and there was no statistically significant difference between the two groups ($p > 0.05$).

It was also similar to other findings, Kumar et al found in 2005 the mean ($\pm$ SD) age of the study group and control group were 28.40 ± 6.24 years and 27.50 ± 5.91 years respectively⁷. Larijani et al observed the mean ($\pm$ SD) for the age of the study group and control group were 27.09 ± 5.24 and 27.04 ± 4.42 years respectively¹⁰. Lao TT et al studies the mean age 28.40 ± 5.20 and 27.50 ± 5.10 years of study and control groups and there was no significant difference between the two groups⁵.

In this study the mean ($\pm$ SD) gestational age at the time of taking blood sample for thyroid hormonal levels was 34.30 ± 2.92 weeks in the study group and 35.10 ± 2.85 weeks was in the control group. The difference between the groups was not statistically significant ($p = 0.55$). The mean ($\pm$ SD) parity of the study group and control group were 1.28 ± 0.90 and 1.30 ± 0.88 respectively and there was no difference between the two groups ($p > 0.05$).

It was also similar to the other studies, Larijani et al found the mean ($\pm$ SD) gestational age was 35.67 ± 6.88 weeks was group and the mean ($\pm$ SD) parity was 2.51 ± 1.43 in the study group and 2.98 ± 1.75 was in the control group¹⁰.

In this research work, the mean ($\pm$ SD) TSH of the study group and control group were 4.14 ± 2.24 mIU/L and 2.75 ± 1.73 mIU/L respectively and there was highly significant different between the two groups ($p = 0.0007$). The mean ($\pm$ SD) T_3 of the study group and control group were 1.95 ± 0.64 nmol/L and 1.98 ± 0.57 nmol/L respectively and there was no difference between the two groups ($p > 0.05$). The mean ($\pm$ SD) T_4 of 128.38 ± 33.43 nmol/L was in the study group and 126.37 ± 34.70 nmol/L was in the control group. The difference between the two groups was not statistically significant ($p > 0.05$).

The mean values of thyroid hormones were with in normal laboratory ranges in both the group. The mean T_3 and T_4 titres were not significantly different in the two groups (T_3 , $p = 0.79$ and T_4 , $p = 0.76$). The mean TSH value was significantly higher in the problematic women than the control ($p < 0.0007$) degree of freedom was 102).

These results were similar to the findings of Kumar et al in the antenatal clinic of a public hospital of Delhi where they found the mean ($\pm$ SD) TSH of the study group and control group were 4.6 ± 3.64 mIU/L and 2.5 ± 2.01 mIU/L respectively and there was highly significant difference between the two groups ($p < 0.001$)⁷.

Lao TT et al in their study found that normotensive women and preeclamptic patients had ignorantly higher TSH ($p < 0.001$) while T_4 and T_3 concentration were slightly low but not significantly lower in the third trimester of pregnancy⁵.

There were similar studies, Larijani reported that the observed reduced serum concentration regarding the T_4 and T_3 reflect the severity of PE. Confirmatory to these report in their study mild cases of PE had lower level of T_3 and T_4 than healthy controls. It had been suggested that the reduced concentration of T_3 and T_4 levels might be explained by the loss of protein and protein bound hormones. Since T_3 is mostly the product of peripheral conversion of T_4 , the involvement of organs such as the liver and kidneys contributes to low level of T_3 ⁸.

In the present study, only TSH is significantly increased in preeclamptic patients at the time of diagnosis as compares to control subjects. The researches findings was also similar to the findings fo the reports that preeclamptic women had higher incidence of biochemical hypothyroidism compares with normotensive pregnant women⁶. Mild alternation in the thyroid hormones might occur due to non-thyroidal illness acting as a stress factor as well as due to decreased plasma albumin concentration in these patients⁹. Serum T_3 and T_4 were decreases significantly and TSH was increased significantly in preeclamptic women in their third trimester¹¹. The titres of T_3 are reported to be significantly related to the decreased plasma albumin concentration in preeclamptic women⁵. It has been suggested that reduced serum concentrations of thyroid hormones in toxemia may be due to the loss of protein and protein-bound hormones in the urine. Modest decreases in thyroid hormones with concomitant increases in TSH levels in maternal serum correlated with severity of PE or eclamptic and high levels of endothelin⁶. The endothelial cell dysfunction plays an important role in the pathogenesis of PE.

In this study TSH levels of both case and control groups were: Out of 52 pregnant women in study group, 21 (40.40%) had higher TSH titers (> 4.8 mIU/L) and 52 pregnant women in control group, 9 (17.30%) of the 30 pregnant women with abnormal TSH titres, had the diagnosis of PE whereas 31 (41.90%) of the 74 pregnant women with normal TSH titers, had PE in the third trimester. This difference between the two groups was found statistically significant ($p = 0.009$), degrees of freedom was 1. Odds Ratio indicates preeclamptic group had change of higher TSH by 3.24 times than the normal group.

The difference in the number of pregnant women of the two groups, having high TSH titres was also significant. More number of preeclamptic women had increased TSH levels at the time of diagnosis when compares with normotensive pregnant women. Kumar et al also observed statistically significant higher number of cases with PE (76.7%) in pregnant women with abnormally high levels of TSH⁷. Diseases of the thyroid gland itself are a predisposing factor for the development of PE¹².

In this study serum TSH level was significantly increased, but there was no alteration in serum level of T_3 and T_4 . Further study with larger sample is suggested to see whether the serum TSH level could be made as a predictor of development of preeclampsia in pregnancy.

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Diabetes Mellitus in Patients with Coronary Heart Disease

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Abstract

Coronary heart disease is the most common form of heart disease and single most important cause of premature death in developed countries. It is estimated that coronary heart disease will become the major cause of death in all regions of the world by 2020. There are several modifiable risk factors of coronary heart disease. Among those diabetes mellitus is one major modifiable risk factor. So we designed this study to see the frequency of diabetes mellitus in patients with coronary heart disease in three tertiary hospitals in Bangladesh with an objective to see the frequency of diabetes mellitus in patients with coronary heart disease. This observational cross-sectional study was conducted in the department of Biochemistry of Bangabandhu Sheikh Mujib Medical University, Dhaka from July 2006 to June 2007. The study was done among 300 purposively selected diagnosed patients of coronary heart disease of both sexes. Diabetes mellitus was diagnosed according to WHO criteria. In this study we found that 23.7% of study subjects had diabetes mellitus. From this study, it can be concluded that the prevalence of diabetes (an important modifiable risk factor) is high in coronary heart disease patients.

Key words: Risk factors, Diabetes mellitus, Coronary heart disease (CHD)

Introduction

Coronary heart disease is a narrowing of the small blood vessels that supply blood and oxygen to the heart¹. It has two principal forms, angina and myocardial infarction (MI). Both angina and MI occur because the arteries carrying blood to the heart muscle become narrowed or blocked, usually by a deposit of fatty substances, a process known as atherosclerosis. Angina is a severe pain in the chest brought on by exertion and relieved by rest. MI is due to obstruction of coronary arteries either as a result of atherosclerosis or by a blood clot. Part of heart muscle is deprived of oxygen and dies².

At different times, the heart has a varying need for blood flow and the oxygen it carries. The heart receives its blood flow through its own set of blood vessels called the coronary arteries. With the relatively decreased blood flow and oxygen, the heart muscle produces chemicals that cause the pain and other symptoms of angina³. MI is the irreversible necrosis of heart muscle secondary to prolonged ischemia. The appearance of cardiac enzymes in the circulation generally indicates myocardial necrosis⁴.

There are several risk factors for the development of coronary heart disease (CHD). Diabetes mellitus is a potential risk factor for CHD⁵. Diabetes mellitus is associated with a four to eight fold excess risk of CHD. Patients with diabetes mellitus have an increased risk of CHD compared with those with normal fasting blood glucose level. Elevation of fasting glucose level is significantly related to CHD morbidity and mortality⁶. Recently, impaired fasting glucose (IFG) was called underestimated risk factor for cardiovascular death. Prevalence of diabetes mellitus in CHD patients differs in various aspects (age, sex etc)⁷. Diabetic patients have increased platelet adhesiveness and increased response to aggregating agents. These changes are likely to favor atherosclerosis in coronary arteries. Atherosclerosis begins to appear in most diabetic patients within a few years of onset of diabetes. Atherosclerosis may result in narrowing or occlusions in coronary arteries and attendant ischemic injury to the heart that may lead to CHD. Diabetes mellitus is one of the important modifiable risk factors for CHD, but there has been limited study addressing frequency of diabetes mellitus in patients with coronary heart disease. For this reason, this study was designed to find out the frequency of diabetes mellitus in patients with CHD.

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Materials and Methods

This observational cross-sectional study was conducted in the department of Biochemistry, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from July 2006 to June 2007. For the study 300 diagnosed patients (209 male and 91 female) of CHD were selected from departments of Cardiology of BSMMU, National Institute of Cardiovascular Diseases (NICVD) and Enam Medical College Hospital, Savar, Dhaka. Consent was taken from all study subjects preserving their rights, privileges and freedom. For estimating blood glucose level, blood was collected in fasting condition and glucose level was estimated by enzymatic assay. Diabetes was defined according to WHO criteria. All data were recorded systematically in a preformed data collection form. Statistical analysis was performed by using SPSS for windows version 12.0.

Results

Out of total 300 CHD patients 209 were male and 91 were female. Mean $\pm$ SD of age was 51.56 ± 24.04 with the range of 25-74 years (Table I). Among the study subjects 71 (23.7%) had diabetes mellitus whereas 227 (76.3%) were nondiabetic (Table II). The mean $\pm$ SD values of fasting blood glucose of diabetic CHD patients and nondiabetic CHD patients were 10.38 ± 2.51 and 4.50 ± 0.56 mmol/L respectively.

Table I: Mean $\pm$ SD of age and sex distribution of study subjects (n=300)

Variables	Number	Percentage	Mean $\pm$ SD (Range)
Age (years)	-	-	51.56 ± 24.04 (25-74)
Sex			
Male	210	70	-
Female	90	30	-

Table II: Frequency of diabetes mellitus in study subjects (n=300)

Status of diabetes	Number	Percentage
Diabetic	71	23.7
Nondiabetic	229	76.3

Discussion

In this study we found that 23.7% of CHD patients were diabetic. Similar type of findings were also observed by Gus et al, in which diabetic patients account for 24% of the coronary heart disease patients⁸. Pyorala et al⁹ reported that the proportion of patients with diabetes was 31% of CHD patients. This proportion is higher than that in our study. In another study in China by Li et al¹⁰ the proportion of patients with diabetes was also found higher (32.8%) compared with our study.

Due to time limitation and financial constraints, we had to conduct this observational cross-sectional study with small sample size. So further studies involving larger sample sizes are recommended.

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Pregnancy in Overt and Subclinical Hypothyroidism and its Feto-Maternal Outcome

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Abstract

This prospective study was done to find out the maternal and fetal complications of pregnancy in patients with subclinical and overt (TSH level higher than subclinical hypothyroidism) hypothyroidism. Chronic hypertension, anemia with GDM, GDM with preeclampsia and thalassemia with GDM were observed only in patients with overt hypothyroidism. PPH, fetal distress, abortion and IUD were significantly higher ($p < 0.05$) in patients with overt hypothyroidism. Fetal distress was found to be more in patients with overt than subclinical hypothyroidism. This study included 50 admitted patients who were pregnant. Among which, 29 were diagnosed as cases of subclinical hypothyroidism and 21 as that of overt hypothyroidism. Duration of marriage was almost identical between two groups. Multipara was predominant in both groups, however abortions were significantly higher ($p < 0.05$) in overt hypothyroidism. Duration between first conception and marriage was somewhat longer (3-5 years) in patients with overt hypothyroidism than that (2 years) in patients with subclinical hypothyroidism. The commonest problem in both groups was anemia. 17.2% of patients with subclinical hypothyroidism were anemic whereas 42.9% patients with overt hypothyroidism suffered anemia. Preeclampsia (23.8%) and diabetes mellitus (38.1%) were also predominant in patients with overt hypothyroidism than in patients with subclinical hypothyroidism (Preeclampsia-3.4% and DM-10.3%). Low Birth Weight (LBW) babies were also common in patients with overt hypothyroidism (80%) than in patients with subclinical hypothyroidism (27.6%). 62.1% of babies from mothers having subclinical hypothyroidism had APGAR score of 7 whereas 73.3% of babies from mothers having overt hypothyroidism had APGAR score of 6 in the first minute. None of the babies were hypothyroid as tested from cord blood. Majority of patients underwent C-section in both groups.

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Introduction

Thyroid disorders are one of the most common endocrine disorders seen in pregnancy¹. Overt hypothyroidism has been reported 1 in 1000 to 1 in 1600 deliveries and subclinical hypothyroidism has been found in 0.19% to 2.5% of pregnancy².

Women with hypothyroidism have relatively high rate of subfertility and miscarriages and carry increased risk for obstetric and fetal complications. The main obstetric complications are anemia, preeclampsia, cardiac dysfunction, placental abruption and postpartum hemorrhage. Fetal complications include prematurity, LBW, fetal distress in labour, fetal death, perinatal death and congenital hypothyroidism³.

Thyroid hormone is essential for fetal development for at least the first half of pregnancy, when the fetus derives the hormone from the mother. Fetal developmental impairment is obvious in maternal hypothyroidism during this time. It is known that, women who are used to be treated with levothyroxine before pregnancy must increase their thyroid hormone replacement by 20% to 40% to keep their thyroid hormone levels within normal range. Most physicians measure the levels of Thyroid Stimulating Hormone (TSH) in early pregnancy and adjust the dose of levothyroxine accordingly. Sometimes, this results in patient becoming transiently hypothyroid before the dose is increased⁴.

Over the past twenty years, there has been a major expansion of our knowledge regarding thyroid disorders accompanying with pregnancy. Simultaneously, a doubling of miscarriage rate has been reported in studies on antibody positive euthyroid women and an increase in preterm delivery has been found in women with subclinical hypothyroidism and/or thyroid autoimmunity⁵.

There has always been lack of agreement regarding the correct reference range to be used, whether TSH or Free Thyroxine (FT4) levels are the most important determinants of normality, impact (Maternal or fetal) of inadequate or excess treatment might be and whether correct treatment can improve neonatal outcome. These difficulties are often further complicated by practical issues like suboptimal pre pregnancy control, late gestation at booking, poor compliance and malabsorption caused by iron and calcium supplementation and pregnancy induced vomiting. Recommendations for management are generally based on expert opinion and even protocols from leading groups are not based on strong evidence and do not concur⁶.

It is generally accepted that, a proportion of women with hypothyroidism need to increase their dose of thyroxin during pregnancy, but it is unclear how their dose changes should be decided. While, some studies suggest that decisions should be based on Thyroid Function Tests (TFT) at the booking visit and during pregnancy and many women would not need an increase if they were taking stable dose of thyroxin during pregnancy⁷, other studies proposed a global increase in the thyroxin dose as soon as pregnancy is confirmed. Moreover, inadequate pre pregnancy control of thyroid function is associated with a need to increase thyroxin dosage during pregnancy. There are concerns that not only it may be unnecessary for many women but also fetal exposure to excess T4 and T3 may be associated with miscarriage and LBW⁸. In cases of treated hypothyroidism (all patients were made euthyroid), none of the babies had congenital anomalies⁹.

This study was carried out to find out maternal and fetal complications during pregnancy with hypothyroidism and to note the pattern of thyroxin dose adjustment.

Materials and methods

This cross sectional study was carried out at the fetal-maternal medicine unit, Department of Obstetrics and Gynecology, BSMMU. Sample size was 50 patients and study period was 6 months. All patients were divided into 2 groups: Group I consisted of patients with subclinical hypothyroidism (elevated TSH with normal T4) and group II consisted of patients with overt hypothyroidism (elevated TSH with low T4). Recently diagnosed hypothyroid pregnant women (either during the study or within 6 months prior to the study) and admitted patients who were diagnosed as overt or subclinical hypothyroid during Antenatal Checkup (ANC) were included in the study. Data were collected with a questionnaire and were analyzed by computer based SPSS (Statistical Package for Social Sciences, Chicago) program, version 16.0.

Results

86.2% of patients in group I conceived for the first time within 2 years after marriage. However, 66.7% in group II conceived within 3-5 years after marriage. Significant difference ($p < 0.05$) was observed in between the two groups regarding number of abortions. 52.4% of patients in group II gave history of 2 abortions whereas, 13.8% patients in group I gave history of 2 abortions. However, 14.3% of patients in group II had history of 3 abortions but none in group I had this history.

Associated medical illnesses were more common in group II patients than in group I. Anemia was the commonest sign found in 17.2% of patients in group I and in 42.9% of patients in group II.

Preeclampsia was found in 3.4% of patients in group I and in 23.8% of patients in group II. Whereas, diabetes mellitus was found in 10.3% of patients in group I and 38.1% of patients in group II. Other medical disorders like chronic hypertension, anemia with GDM, GDM with preeclampsia and thalassemia with GDM were observed only in group II patients.

History of thyroxin intake revealed 55.2% of study patients received 50µg of thyroxin per day in group I. However, 71.4% of patients in group II received 150µg thyroxin per day.

Complications during delivery were observed mostly in group II patients. Impending eclampsia was found in 3.4% of patients in group I and in 19.0% of patients in group II. Prolonged second stage of labour was more common in group II (42.9%) than in group I (13.8%) patients. Fetal distress was also more frequent in group II (80.9%) patients compared to that in group I (41.4%) patients. PPH, abortion and IUD were observed only in group II patients.

The mean TSH level (mean±SD) in group I patients was 12.6 ± 19 µIU/ml and that in group II patients was 13.9 ± 10.4 µIU/ml during the first trimester of pregnancy which was not statistically significant ($p > 0.05$) according to unpaired t-test. However, mean TSH level at the second trimester of pregnancy was 0.41 ± 0.7 µIU/ml in group I patients and 0.93 ± 0.23 µIU/ml in group II patients, which was statistically significant ($p < 0.05$) as determined by unpaired t-test. During third trimester of pregnancy, mean TSH level was 2.0 ± 1.1 µIU/ml in group I patients and 2.9 ± 1.3 µIU/ml in group II patients - which was found statistically significant by unpaired t-test.

Regarding mode of delivery, majority of the study patients underwent LUCS in both groups, which was 24 (82.8%) in group I and 15 (83.3%) in group II. There were 3 abortions, out of which, 2 required evacuation under anesthesia.

Considering fetal outcome, it was observed that, 27.6% and 80.0% of the babies had LBW (fetal weight < 2.5 kg) in group I and group II respectively. In group I, 62.1% of the babies had APGAR score of 7 but in group II, 73.3% of the babies had that of 6 at the 1st minute. During the 5th minute, APGAR score was 7 in 86.2% and 80.0% of babies in group I and group II respectively. Only 13.8% of babies in group I and 20.0% of babies in group II were sent to NICU. Cord blood investigation revealed no hypothyroidism in any of the test subject. Birth weight and APGAR score at the 1st minute revealed statistically significant ($p < 0.05$) difference between groups, but others were non-significant ($p > 0.05$).

Discussion

In this study, we observed that, 62.1% of the patients were in the age range of 15 to 24 years in the group containing patients with subclinical hypothyroidism and 66.7% of the patients were in the age range of 25 to 44 years in the group containing patients with overt hypothyroidism. Age ranges of 15 to 24 years and 25 to 44 years were significantly ($p<0.05$) higher in patients with subclinical hypothyroidism and overt hypothyroidism respectively compared to control. This result resembles other study results showing higher maternal age in hypothyroid women^{1,7,9}.

Studies have shown that, pregnant women with hypothyroidism usually have high rate of multiple abortions or miscarriages⁹. We also had significantly ($p<0.05$) high rate of multiple abortions among our study subjects.

Previous studies have shown that, patients with overt hypothyroidism had high rate of gestational diabetes and neonatal complications in the form of birth asphyxia, jaundice, hypoglycemia etc. needing admission into NICU¹. Our study results also have close resemblance to the fact. Most of the women with hypothyroidism, who are on maintenance dose of thyroxin, require an increase in the dose during pregnancy - as stated by previous work⁹. 71.4% of patients with overt hypothyroidism in this study, required increase in dose of thyroxin.

As we stated above, maternal complications are significantly higher in most of the patients with overt hypothyroidism, other studies have also stated the same⁹. Fetal complications were almost the same as described by others^{10, 11} and no significant association was found between cord blood study and maternal TSH¹.

Though the study has helped us correlate the facts related to hypothyroidism in pregnancy and its outcomes in mother and fetus, it is a comparative study and thus it has its limitations. Further investigations in each of the segments of the study are necessary to reveal the exact mechanisms of different outcome in maternal hypothyroidism.

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Comparative Study of Post Operative Astigmatism Following Small Incision Cataract Surgery-Sics in Superior, Supero-Temporal and Temporal Incision.

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Abstract

This prospective study was designed to evaluate and compare surgically induced astigmatism in small incision cataract surgery through superior, supero-temporal and temporal approach.

Astigmatism means no point focus. It is a refractive error that occurs when the optical system does not have the same refractive power at all its meridian. The location and width of incision will determine the amount of surgically induced astigmatism (SIA) in small incision cataract surgery. Temporal and superotemporal incisions are less likely to induce post operative astigmatism than the 12 o' clock incisions.

The study was carried out at Tairunnessa Memorial Medical College and Hospital, Gazipur, Faridpur Diabetic Association Medical College and Hospital, Faridpur and General Hospital, Faridpur, Bangladesh, from January 2012 to June 2013. Total number of 120 eyes of 108 patients, both male and female patients were included for the study. We excluded the patients having corneal scar, irregular astigmatism, presence of pterygium and previous intraocular surgery from our study. The mean patient age at the time of surgery was 61.9 ± 8.1 years ranged from 40 to 70 years. The patients were divided into three groups. The three groups had 40 patients each. The patients in group-A underwent manual SICS with a superior incision, the patients in group-B underwent manual SICS with a supero-temporal incision and the patients in group-C underwent manual SICS with a temporal incision. The small incision cataract surgeries were done by applying same surgical technique. The courses of the post operative astigmatic changes were determined by using Auto Refracto Keratometer at 1st week, 6th weeks and 12th week postoperatively.

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The mean surgically induced astigmatism- SIA in group-A was found to be 1.45 ± 0.44 , in group- B, it was 1.08 ± 0.44 and in group-C, it was 0.08 ± 0.34 .

Small incision cataract surgery-SICS with a temporal and superior-temporal approach provides earlier stabilization of refraction and better visual acuity due to significantly less SIA than the superior approach.

Keywords: Astigmatism, Small incision cataract surgery, Superior incision, Temporal incision, Supero-temporal incision, Surgically induced astigmatism (SIA)

Introduction

Cataract is the leading cause of avoidable blindness specially in the developing country accounting for about three quarters of the blindness. The mainstay of the management of cataract is surgery. Cataract surgery is no more a blind rehabilitation surgery. But it gives absolutely a normal vision. Cataract surgery has undergone great refinement in recent years. Recent progress in cataract surgical technique have heightened patient's expectation of visual outcome; good post-operative vision without spectacles is considered normal. Small incision cataract surgery-SICS, is a simple and versatile technique which unlike phacoemulsification can be universally applied nearly all type of cataract. Lack of suture tension can lead to astigmatic shift against the rule. Surgically induced Astigmatism(SIA) is one of the important factors that hampers post-operative good visual outcome. Thus control of post-operative astigmatism is a key factor in meeting these expectation.

Materials & Methods

The study was carried out at Tairunnessa Memorial Medical college and Hospital, Gazipur, Faridpur Diabetic Association Medical College and Hospital, Faridpur and General Hospital, Faridpur, Bangladesh, from January 2012 to June 2013.

Total number of 120 eyes of 108 patients, both male and female patients were included for the study. We excluded the patients having corneal scar, irregular astigmatism, presence of pterygium and previous intraocular surgery from our study. The mean patient age at the time of surgery was 61.9 ± 8.1 years ranged from 40 to 70 years.

We measured the pre-operative corneal astigmatism by using Auto Refracto Keratometer. We carried out the measurement at least two times for each. The patients were divided into three groups. The three groups had 40 patients each. The patients in group A underwent manual SICS with a superior incision, the patients in group B underwent manual SICS with a supero-temporal incision and the patients in group C underwent manual SICS with a temporal incision.

Small incision cataract surgeries were done by applying same surgical technique in three the groups. Cataract extraction was done in these patients under peri-bulbar anesthesia using a sclero-corneal tunnel incision, which is 6.5 mm long in sclera, 8 mm inside cornea, 2 mm behind the limbus and 1 mm into the cornea.

Continuous curvilinear capsulorhexis performed followed by hydro procedures and finally nucleus was delivered by sandwich method. Intraocular lens was placed in the bag. Surgical section was closed by self-sealing method forming the anterior chamber with ringers lactate solution. The courses of the post operative astigmatic changes were determined by performing Auto Reracto Keratometer at 1st week, 6th weeks and 12yh weeks postoperatively.

Results

The results are shown in tabulated form below:

Table-I : Shows distribution of age among the study group.

Age in years	Group-A		Group – B		Group-C	
	No.	(%)	No.	(%)	No	%
41- 50	3	7	2	5	2	5
51-60	18	45	17	42	13	32
61- 70	19	48	21	53	26	63

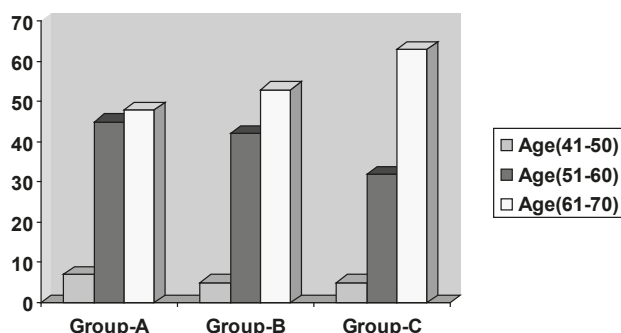


Fig-1: Bar diagram shows distribution of age among the study group.

Table-II : Shows distribution of pre-operative astigmatism among the study group. Difference of mean pre-operative astigmatism between three groups were statistically not significant.

Pre-operative astigmatism (Dioptre – D)	Group-A		Group – B		Group-C	
	No.	(%)	No.	(%)	No	%
00 – 0.5	02	42.50	05	45	03	
0.51 – 1.0	14	35	15	32.50	18	
1.1 – 1.5	18	17.50	17	20	14	
1.51 – 2.0	06	4	03	2.50	05	
Mean astigmatism (Dioptre – D)	0.63D		0.59D		0.61D	

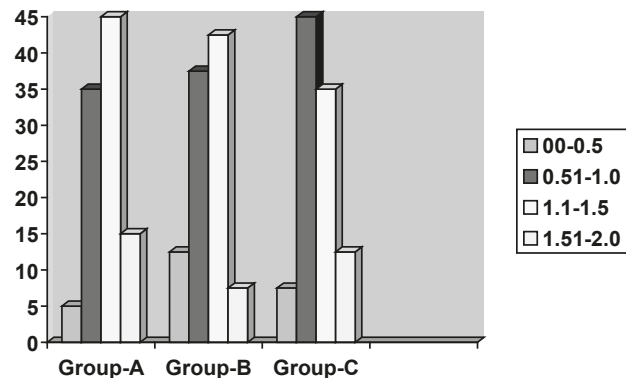


Fig-2: Bar diagram shows distribution of pre-operative astigmatism among the study group.

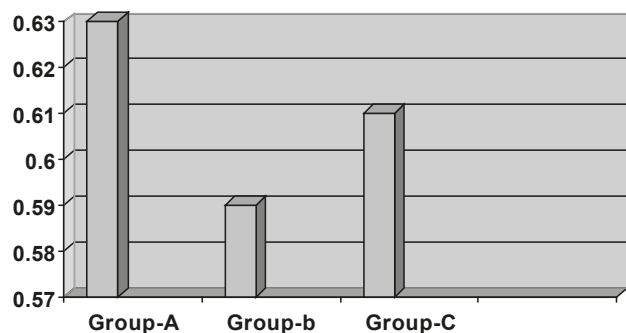


Fig-3: Bar diagram shows pre-operative mean astigmatism among the study group. The pre-operative mean astigmatism was 0.63D in Group -A, in Group- B it was 0.59D and in Group- C it was 0.61D.

Table-III: Shows the distribution of mean surgically induced post-operative astigmatism among the study group.

Post-operative period	Group-A	Group – B	Group-C
	Mean astigmatism. (± SD)	Mean astigmatism. (± SD)	Mean astigmatism. (± SD)
1 st week	1.83 (± 0.45)	1.47 (± 0.44)	1.32(± 0.37)
6 th week	1.63 (± 0.44)	1.23 (± 0.43)	1.12(± 0.35)
12 th week	1.45 (± 0.44)	1.08 (± 0.44)	0.88(± 0.34)

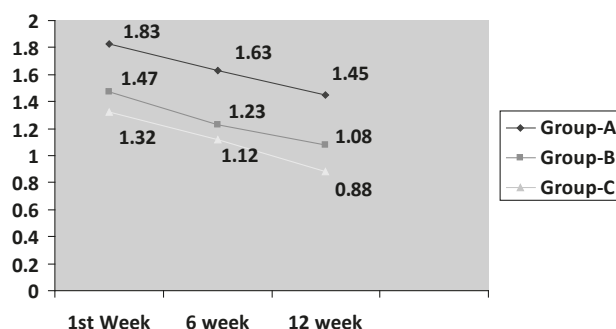


Fig-4: Line chart shows the distribution of mean surgically induced post-operative astigmatism among the study group.

Discussion

The success of cataract surgery either small incision cataract surgery or phacoemulsification is determined by quicker visual and functional recovery. Control of post-operative surgically induced astigmatism (SIA) is a key factor in meeting the expected visual outcome. The astigmatism which was induced in small incision cataract surgery- SICS which was done with superior, supero-temporal and temporal scleral tunnel incisions was compared. This study found that the surgically induced astigmatism was lower in the temporal and supero-temporal groups as compared to that in the superior group.

In our study the mean SIA in group A, was found to be 1.45 ± 0.44 , in group B, it was 1.08 ± 0.44 and in group C, it was 0.88 ± 0.34 . Vaishali Satyajeet Pawar et al¹, showed that surgically induced astigmatism (SIA) in the superior group was 1.57 ± 0.61 , it was 0.53 ± 0.31 in the superotemporal group and it was 0.43 ± 0.31 in the temporal group. Pawar VS et al² observed that the mean SIA in superior group was found to be 1.572 ± 0.651 , in supero-temporal group, it was 0.532 ± 0.317 and in temporal group, it was 0.435 ± 0.338 .

In the study of Gokhale NS et al³, found the SIA in the superior group was 1.28D, it was 0.2D in the superotemporal group and it was 0.37D in the temporal group. Radwan AA⁴, observed in his study mean surgical-induced astigmatism (SIA) was found to be significantly lower in the temporal group compared to that in the superior group. The superior incision induced 2.1 D of "against the rule astigmatism(ATR)". While the temporal While the temporal incision induced 0.7 D of WTR astigmatism.

Kohnen et al⁵, Simsek et al⁶, Oshima et al⁷ Cillino S et al⁸ and Mendivil et al⁹ also showed that surgically induced astigmatism (SIA) is more in the eyes that received superior incisions than that of temporal incisions and this difference was statistically significant. This study found that the surgically induced astigmatism-SIA was lower in the temporal and supero-temporal groups as compared to that in the superior group.

Small Incision Cataract Surgery (SICS) is a good alternative to Phacoemulsification but the rates of astigmatism are higher due to the larger sizes of the incisions. When the incision is located superiorly, both the gravity and the blinking of eyelid tend to create a drag on the incision. These forces are neutralized better with temporally placed incisions because in

The temporal location is the farthest from the visual axis and any flattening which is caused by the wound is less likely to affect the corneal curvature at the visual axis. A temporal incision is advantageous because it can be made easily in deep sockets and small eyes. The "against the rule drift" is present more markedly in SICS patients with superior tunnel approach than that of temporal tunnel due to various reasons. First an "against the astigmatism" predominantly present in cataract age group and it is further increased with an incision at 12 o'clock meridian. Next, the eyelid pressure emphasizes the "against the rule shift" with a 12 o'clock incision in the elderly population. Considering all these points, SICS with temporal tunnel approach is a better option for large volume cataract surgery.

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Addiction and Liver Disease

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Abstract

Drug induced liver disease is a global problem. The aims of the study are to know the recreational drugs causing harmful effect on liver, epidemiology of addiction; pathophysiology and their consequences.

The major findings published to date concerning different agents causing addiction and liver disease, their implications with regard to understanding disease mechanisms and their amplitude or spectrum are described.

Addiction not only invites lot of sufferings to the family and the country, but also responsible for different types of liver disease including fatty liver, hepatitis and liver failure; responsible for mortality and morbidity. Among the addiction causing substances alcohol playing the main role for liver disease worldwide. Indirect effects of addiction on liver are hepatitis B, hepatitis C and their complication, mainly due to contamination of sharing needle. Majority of people in Bangladesh are life long abstainer.

Excessive alcohol beverages and other substances like heroin, amphetamine are not harmless, rather they can cause serious liver diseases. There are some differences in prevalence of addiction and liver diseases among countries. Intravenous drug users are affected both directly and indirectly due to contaminated needle sharing.

Introduction

The liver is an important organ in the human body. It is the largest gland and plays a key role in the removal of toxins and lipophilic materials from the plasma. When this liver is exposed to toxic substances particularly due addiction such as alcohol with an excess, it becomes sick.

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Addiction is a global problem which is a compulsive act causes harm to the person and those around them and over which the person no longer has control. For an example a person who constantly drinks excess alcohol in spite of the fact that it is hurting his family and career. An addict may deny it, rather state they are, "just enjoy". Addiction is the continued use of a mood altering substance or behaviour despite adverse dependency consequences¹, or a neurological impairment leading to such behaviors².

The American Society of Addiction Medicine (ASAM) has published a definition of addiction highlighting that addiction is a chronic brain disorder and not simply a behavioral problem involving too much alcohol, drugs. ASAM has taken an official position that addiction is not solely related to problematic substance use³.

Characteristics of addiction:

(a). Inability to consistently abstain; (b). impairment in behavioural control; (c). craving; or increased "hunger" for drugs or rewarding experiences; (d). diminished recognition of significant problems with one's behaviors and interpersonal relationships; (e) a dysfunctional emotional response⁴.

List of Addictions to Substances:

Substance use disorders in the DSM-IV-TR provide a list of addictions relating to the following substance:

- Alcohol
- Tobacco
- Opioids (like heroin)
- Prescription drugs (sedatives, hypnotics, or anxiolytics like sleeping pills and tranquilizers)
- Cocaine
- Cannabis (marijuana)
- Amphetamines (like methamphetamine, known as meth)
- Hallucinogens
- Inhalants
- Phencyclidine (known as PCP or Angeldust)
- Other unspecified substances⁵

Type of addiction causing liver disease:

Alcohol:

Among the substances causing addiction, alcohol is the most important one causing liver disease worldwide. Alcohol dependence is a powerful mechanism sustaining alcohol consumption and thus impacting on both chronic and acute consequences of alcohol, though it is also a

The clinical history which may suggest alcohol abuse or alcohol dependence includes the pattern, type, and amount of alcohol ingested, as well as evidence of social or psychological consequences of alcohol abuse⁷. Alcoholic liver disease ranging from fatty liver to hepatic inflammation and necrosis (alcoholic hepatitis) to progressive fibrosis (alcoholic cirrhosis)⁸. Alcohol causes 1.8 million deaths (3.2% of total) and a loss of 58.3 million (4% of total) of Disability-Adjusted Life Years⁹.

Overall there is a causal relationship between alcohol consumption and more than 60 types of disease and injury. Alcohol is estimated to cause about 20-30% of oesophageal cancer, liver cancer, cirrhosis of the liver worldwide¹⁰.

Prevalence of alcohol addiction:

Alcohol consumption and addiction is prevalent worldwide, but quality varies in different parts, as well as urban and rural areas. The true prevalence is unknown, but histologic studies of patients with ALD suggest that alcoholic hepatitis may be present in as many as 10%-35% of hospitalized alcoholic patients^{11,12,13}. The World Health Organization (WHO) estimates about 2 billion people worldwide who consume alcoholic beverages and 76.3 million with diagnosable alcohol use disorders⁹.

In the 1993 National Household Survey, 21.7% of Asian American and Pacific Islanders had smoked cigarettes, 53.2% had used alcohol¹⁴. Asian Pacific Islanders had the lowest percentages of alcohol dependence (1.8%), need for drug treatment (1.7%), and heavy alcohol use (0.9%)^{15,16}.

Total lifetime abstainers in Bangladesh as measured by the 2003 World Health Survey is estimated to be 94% of the total population; 87.4% of male Bangladeshis are abstainers and likewise, 99.7% of female Bangladeshis are abstainers¹⁷.

Approximately 7.4% of adult Americans were estimated to meet DSM-IV criteria for the diagnosis of alcohol abuse and/or alcohol dependence in 1994¹⁸; Alcohol is commonly used in USA and approximately two-thirds of adult Americans drink some alcohol¹⁹.

Another more recent data suggest 4.65% meet criteria for alcohol abuse and 3.81% for alcohol dependence²⁰. However, geographic variability exists in the patterns of alcohol intake throughout the world²¹. The majority drink small or moderate amounts and do so without evidence of clinical disease^{22,23,24}. A subgroup of drinkers, however, drink excessively, develop physical tolerance and withdrawal, and are diagnosed with alcohol dependence²⁵. In Australia, prevalence of DSM-IV alcohol abuse and dependence by gender: Harmful use in males- 4.3%, dependence 5.2%, whereas in females it is 1.8.²⁶

Alcohol is also commonly consumed in Australia; 83% of the population in the 2007 Drug Strategy Household Survey aged over 14 years reported drinking alcohol in the previous 12 months²⁷.

Spectrum of alcoholic liver disease:

Alcohol is responsible for significant disability as well as it kills many people in the world. The most prevalent types of alcoholic liver disease are fatty liver, alcoholic hepatitis, and cirrhosis. Fatty liver may be a less problematic and reversible if abstinence is maintained. Often, as people continue to drink heavily, they progress from fatty liver to hepatitis to cirrhosis. The disorders can also occur together, however, and liver biopsies can show signs of all three in some people²⁸. Furthermore, sustained excessive alcohol intake may be the cause of the progression of other liver diseases, such as virus-related chronic hepatitis, also increasing the risk of hepatocellular carcinoma^{21,29,30}.

Although not invariable, fatty liver develops in about 90% of individuals who drink more than 60 g/day of alcohol³¹. According to another study report, about 20 percent of alcoholics and heavy drinkers develop fatty liver, or steatosis. In many cases there are no clinical symptoms except for an enlarged liver (hepatomegaly). Fatty liver can be reversed if alcohol consumption is stopped or significantly reduced³².

These are not necessarily distinct stages of evolution of disease, but rather, multiple stages that may be present simultaneously in a given individual^{33,34}. However, alcohol dependency per se is not always a pre-requirement for ALD development³⁵. In fact, some patients develop ALD, particularly, cirrhosis, without a history of dependence. Moreover, the severity of disease does not always correlate with the amount of alcohol intake, and environmental and genetic factors likely play a crucial role in ALD development^{36,37}.

Daily ethanol consumption exceeding 40-80 g/day for males and 20-40 g/day for females for 10-12 years will almost certainly lead to ALD^{38,39,40}. It is shown that women have been found to be twice as sensitive to alcohol-mediated hepatotoxicity and may develop more severe ALD at lower doses and with shorter duration of alcohol consumption than men⁴¹.

Likewise, heavy drinking in combination with hepatitis B or C substantially increases the risk of liver cirrhosis, compared with the risk associated with heavy drinking alone⁴². For example, people with alcohol-related cirrhosis are at much higher risk for the development of liver cancer⁴³.

Liver cirrhosis is an irreversible condition which is a long term effect of alcohol consumption and this cirrhosis is a major cause of death in the United States⁴⁴. In 2000, it was the 12th leading cause of death, accounting for 1.1 percent of all deaths³². In 2003, 44% of all deaths from liver disease were attributed to alcohol⁴⁶. In Europe alone, alcohol consumption was responsible for over 55 000 deaths among young people aged 15-29 years in 1999⁴⁷.

Mortality studies have demonstrated that heavy drinkers and alcoholics die from cirrhosis at a much higher rate than the general population^{40,48,49,50}. Alcohol has consistently been related to the risk of malignancy like cancer of the mouth (lip, tongue), pharynx, larynx, hypopharynx, oesophagus and liver⁵¹⁻⁵⁴.

Pathophysiology of alcohol toxicity:

Liver disease in the alcoholic is due not only to malnutrition but also to ethanol's hepatotoxicity linked to its metabolism by means of the alcohol dehydrogenase and cytochrome P450 2E1 (CYP2E1) pathways and the resulting production of toxic acetaldehyde. In addition, alcohol dehydrogenase-mediated ethanol metabolism generates the reduced form of nicotinamide adenine dinucleotide (NADH), promotes steatosis by stimulating the synthesis of fatty acids and opposing their oxidation. Steatosis is also promoted by excess dietary lipids and can be attenuated by their replacement with medium-chain triglycerides⁵⁵.

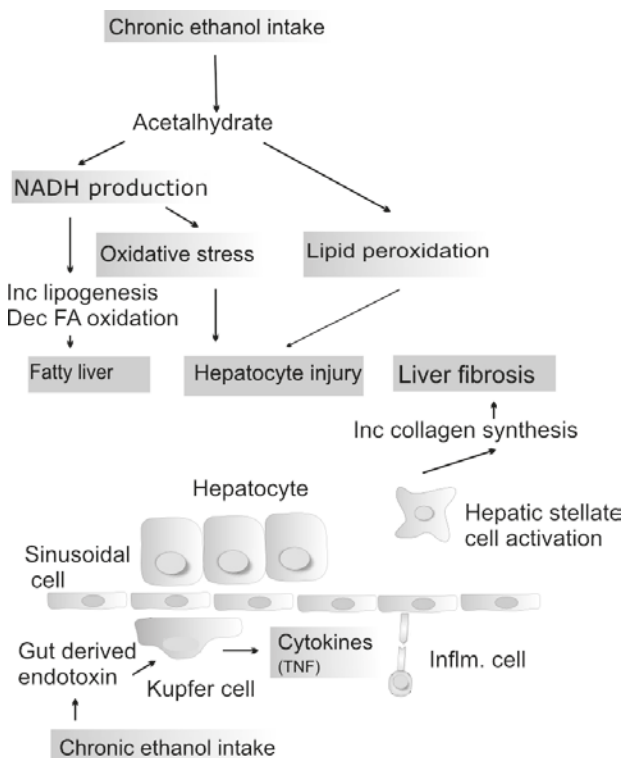


Figure: Pathogenesis of alcohol induced liver injury⁵⁶

According to reports, genetic predisposition to ALD has clearly emerged. Family, twin and adoption studies have convincingly shown that genetic determinants play an important role in the development of alcohol dependence and alcohol-related disorders with heritability estimates in the range of 50-60%⁵⁷⁻⁶⁶.

Alcohol also affects the energy production. The rate of ATP synthesis in liver cells exposed to ethanol is typically reduced⁶⁷. Chronic alcohol consumption depresses the activity of all mitochondrial complexes, except complex II, as several abnormalities in mitochondrial respiratory chain have been described in experimental models of chronic ethanol intoxication^{68,69}. Alcohol consumption causes free radical generation that damages DNA⁷⁰, which is repaired by the base excision-repair pathway involving DNA ligase III, DNA polymerase β and poly(ADPribose) polymerase.

Liver has tremendous power of repairing the damage. Reduced repair of DNA lesions represents an important risk factor for the development of ALD. Many of polymorphisms in several DNA repair genes have been identified^{71,72,73}.

Alcohol consumption can impair the immune response. Alcohol intake increases the intestinal permeability to a variety of substances that include bacterial endotoxins such as lipopolysaccharide⁷⁴. Lipopolysaccharide 'sensitises' Kupffer cells by binding with the CD14 receptor. This bond activates the nuclear factor kappa B (NF- κ B) which, in turn, causes exaggerated transcription of pro-inflammatory cytokines such as TNF- α , IL-6 and transforming growth factor beta (TGF- β)^{74,75,76}.

The risk factors for alcoholic liver disease(ALD):

Quantity : Alcohol consumption of 60-80g per day (about 75-100 ml/day) for 20 years or more in men, or 20g/day (about 25 ml/day) for women significantly increases the risk of hepatitis and fibrosis by 7 to 47%^{7,21}.

Drinking pattern: drinking of alcohol outside of meal times increases up to 2.7 times the risk of alcoholic liver disease⁷.

Female gender: Females are as twice as men susceptible to alcohol related liver disease, and may develop alcoholic liver disease with shorter durations and doses of chronic consumption. The lesser amount of alcohol dehydrogenase secreted in the gut, higher proportion of body fat in women, and changes in fat absorption due to the menstrual cycle may explain this phenomenon⁷⁷. **Hepatitis C infection:** a concomitant hepatitis C infection significantly accelerates the process of liver injury⁷⁷.

Genetic factors: genetic factors predispose both to alcoholism and to alcoholic liver disease. Monozygotic twins are more likely to be alcoholics and to develop liver cirrhosis than dizygotic twins. Polymorphisms in the enzymes involved in the metabolism of alcohol, such as ADH, ALDH, CYP4502E1, mitochondrial dysfunction, and cytokine polymorphism may partly explain this genetic component. However, no specific polymorphisms have currently been firmly linked to alcoholic liver disease^{57,66}.

Iron overload (hemochromatosis): Iron plays a role in the genesis of ALD^{37,78}

Dietary factor: Malnutrition like vitamin A and E deficiencies may worsen alcohol-induced liver damage by preventing regeneration of hepatocytes. This is particularly a concern as alcoholics are usually malnourished because of a poor diet, anorexia, and encephalopathy⁷⁷.

Nutritional effect of alcohol:

Although previously thought that alcoholic liver disease was attributed exclusively to dietary deficiencies, but clinical studies have now established alcohol's hepatotoxicity⁷⁹. Despite an adequate diet, it can contribute to the entire spectrum of liver diseases, mainly by generating oxidative stress through its microsomal metabolism via cytochrome P4502E1 (CYP2E1). It also interferes with nutrient activation, resulting in changes in nutritional requirements⁷⁹. Nutritional deficiencies coupled with alcohol consumption can favour the development of ALD. It is also found that malnutrition is common in a l c o h o l i c s⁸⁰.

Amphetamines:

Amphetamine is one of the most important substance causing addiction. The use of "ecstasy" or Methylenedioxymethamphetamine (MDMA) as a recreational drug is increasing in Europe since the 1980's. Aside intended psychological effects the use of ecstasy can be followed by symptoms of intoxication; complications include toxic hepatic damage up to acute hepatic failure⁸¹.

The "ecstasy"-induced hepatotoxicity can occur dose-independently with a symptom-free period from days to weeks after ingestion, although etiopathology is not yet fully understood⁸¹. Although various estimates have been given on the extent of current illicit MDMA use in the United States and western Europe, the exact prevalence remains unknown. According to the 2004 National Drug Use and Health, more than 11 million persons aged 12 years and older have reported using MDMA at least once in their lifetimes⁸².

Drug Abuse Warning Network (DAWN) data have shown a steady increase in emergency department (ED) visits from MDMA abuse. The DAWN estimates have shown a greater than 800% increase since 1995 from 421 ED visits to 4,026 in 2002 and another 167% increase in 2005 with 10,752 ED visits. These are collected from hospitals in major metropolitan areas throughout the United States and reflect trends of drug abuse and not national numbers⁸³.

According to a 1993 National Institute on Drug Abuse survey, 2% of all US college students admitted to taking MDMA in the previous 12 months. Study of Stanford University undergraduate students reported that 39% had taken MDMA at least once in their lives. But another data from Tulane University survey of more than 1200 students shows 24% had used MDMA⁸⁴.

Although direct toxic effect of MDMA to the liver is unclear, hepatitis and liver failure have been reported. It is interesting that a subset of the population may be at risk for liver toxicity. These patients are missing a liver enzyme called CYP2D6, which is necessary to metabolize MDMA. It is deficient or totally absent in 5-10% of whites and African Americans and in 1-2% of Asians⁸⁵.

Hepatotoxicity ranges from asymptomatic liver injury with abnormal liver function tests to fulminant acute hepatic failure. Different patterns of liver injury including benign lesions, viral hepatitis, extensive or focal hepatic necrosis, total loss of liver parenchyma and function with accompanying encephalopathy, cerebral edema, and multiorgan system failure are evidenced⁸⁵. High doses of amphetamines can be associated with liver injury and distinctive forms of liver injury which has been most commonly associated with MDMA: "ecstasy"⁸⁶.

Although amphetamine has not been invariably associated with serum aminotransferase elevations, there have been several case reports of clinically apparent acute liver injury attributed to the amphetamines; particularly MDMA has been implicated in a large number of cases of acute liver injury which can be severe and lead to acute liver failure and death⁸⁶.

As mentioned before that the onset of ecstasy-associated hepatitis is generally 3 to 14 days after ingestion and abrupt onset with fatigue, weakness, jaundice and confusion. The pattern of serum enzyme elevations is typically hepatocellular and ALT and AST values may be markedly increased with similar increases in lactic dehydrogenase. There is often an early presentation with acute liver failure and prolongation of the prothrombin time and other organ injury is often present⁸⁶.

The clinical course and early histological features of ecstasy-induced hepatitis are similar to the patterns that occur with ischemic hepatitis and liver injury due to hyperthermia⁸⁵. In grade III or IV hepatic encephalopathy induced by MDMA, without a liver transplant, the mortality rate is more than 50%. The timing of ingestion and onset of symptoms, as well as doses, do not seem to correlate with the clinical severity, and recurrence can also occur due to chronic use. Chronic use of MDMA leads to fibrotic changes that are related to an increase of collagen I production by the stellate cells⁸⁵.

Amphetamines undergo extensive hepatic metabolism largely by the hepatic P450 system (CYP 2D6) and generation of a toxic metabolite may cause of hepatic injury with high doses. In cases of hyperacute liver failure due to ecstasy and to intravenous amphetamine, hyperthermia, shock and ischemia may account for the early liver injury⁸⁶.

Addiction and viral hepatitis:

Intravenous drug addiction by sharing of contaminated needle is very much important risk factor for the development of liver disease, particularly hepatitis B and hepatitis C. Globally, 90% of new hepatitis C infections are attributed to injection drug use⁸⁷. Among them ~90% in Australia, ~72% in Canada, and ~54% in the United States are contracted through injection drug use as the major risk factor for HCV infection⁸⁸⁻⁹².

HBV and HCV infections are also acquired relatively rapidly among IDUs. Within 5 years of beginning injection drug use, 50%-70% of IDUs become infected with HBV. Between 50%-80% of IDUs become infected with HCV within 5 years of beginning injection drug use; it is usually the first bloodborne virus they acquire⁹². Among the countries in Asia HBV prevalence was 6.5% detected amongst Kabul IDUs⁹³.

Morphine and its derivatives addiction:

Heroin is a derivative of morphine. Heroin, diacetylmorphine, is produced through morphine acetylation at loci 3 and 6. Wright synthesized it in 1874, the event that was warmly welcomed by the medical profession due to the fact that heroin could be used as a possible substitute for morphine and codeine⁹⁴.

In 1895, the German drug company Bayer marketed diacetylmorphine as an over-the-counter drug under the trademark name Heroin⁹⁵. Heroin is a highly addictive drug, and its use is a serious problem in America. Current estimates suggest that nearly 600,000 people need treatment for heroin addiction⁹⁶.

Estimated worldwide prevalence of current opioid use in 2009 was between 0.3% and 0.5%, equating to 21 to 35 million people, including nearly 18 million people (5.9% of the population) in the United States⁹⁷. In Asia, heroin addiction spread first to the populations of capital cities and then to other cities and towns and even to the hill tribes in Thailand have revealed. Most recent studies have shown that heroin abuse has spread further in Asia, both socially and geographically, involving such countries as India and Sri Lanka⁹⁸.

An estimated 4.1 million people (1.6%) in the United States have used heroin at least once in their lives, and at least 359,000 are believed to be addicted to the drug^{99,100}.

Substantial regional differences in abuse patterns exist. In the majority of Europe, Africa, and Asia, heroin is the most prevalent illegally consumed opioid. However, some African and Asian nations have reported a surge in prescription opioid abuse in the last decade^{97,101}.

Traditional opium-cultivating countries and their neighbors contain the majority of raw opium users. Although comprising less than 5% of the world population, Americans consume roughly 80% of the global opioid supply¹⁰².

Intravenous (i.v.) heroin intake leads to significant morphological changes in the liver tissue (vesicular changes, fat changes, chronic hepatitis, cirrhosis). The intensity of these changes increases with duration of heroin usage¹⁰³.

Hepatocyte is the main locus of the bio-transformational systems which, through the action of the enzymes, enable the removal of the metabolites of these compounds from the organism. During these processes, ultrastructural hepatocyte changes and toxic liver damage occur, and intravenous intake of heroin leads to severe hepatic tissue infections (hepatitis, AIDS). The effects of heroin intake are most pronounced in the liver¹⁰³.

The morphologic changes in the liver tissue are associated with its function

disturbances, which results in the altered metabolism of heroin and other toxins taken simultaneously (alcohol, drugs) and, if these substances are abused, leads to the effects that are often surprising¹⁰⁴⁻¹⁰⁶.

The functional disorder of the liver increases hemato-encephalic barrier permeability, thus enabling neuroactive substances to reach the brain cells in enormous amounts^{107,108}.

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Drug Addiction in Bangladesh and its Effect

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Abstract

Drug addiction and drug abuse, chronic or habitual use of any chemical substance to alter states of body or mind for other than medically warranted purposes. Addiction is more often now defined by the continuing, compulsive nature of the drug use despite physical and/or psychological harm to the user and society and includes both licit and illicit drugs, and the term "substance abuse" is now frequently used because of the broad range of substances (including alcohol and inhalants) that can fit the addictive profile. Psychological dependence is the subjective feeling that the user needs the drug to maintain a feeling of well-being; physical dependence is characterized by tolerance (the need for increasingly larger doses in order to achieve the initial effect) and withdrawal symptoms when the user is abstinent. There are a lot of effects of drug addiction to the economy, society, and family. Drug addiction affects individual's physical and mental health. Drug addicts are burden for a family and society. It is a great challenge for all nations of the world to prevent drug addiction. This article reviews the effects of drug addiction in details.

Introduction

World Health Organization (WHO) defines Drug; it is a chemical substance of synthetic, semi synthetic or natural

origin intended for diagnostic, therapeutic or palliative use or for modifying physiological functions of man and animal.

Drug addiction is now prevalent everywhere in Bangladesh; in the house, streets, in the workplace, parks, slums, markets and even in educational institutions both in rural and urban areas. Virtually all segments of society are severely affected by this problem. Near about 25 lakh people are drug addicted. In Bangladesh about 80 percent of the drug addicts are adolescents and young men of 15 to 30 years of age.

The spread of multiple drug use has aggravated the overall problem, personal and social days function, impairment of health, crime and other violent behavior.

Young people abuse drugs due to complex social and peer groups influence, frustration, depression, curiosity, sub-cultural and psychological environment that induce the youths to take drugs. Major risk factors responsible for drug abuse are family disorganization, parental neglect, parent-child conflict, loss of spouse strife, indiscipline, isolation, lack of emotional support, rejection of love, over protection, unemployment, repeated failure and personality mal adjustment and easy availability of drugs.

Effects of drug abuse know no bound. There are physical, psychological, familial, social, economic and National effects. Drug addiction leads to disintegration of family lies. The drug addicts in a threat to the family Because of the hostile behavior of the drug abuser the family in at risk. Normal activities of the family disrupts due to antisocial activities of the abuser. The drug addict youth drops out from school/college or university education. The service holder loses his job because of irregularities. Social isolation and alienation are very common. Family of the drug addict became isolated from the community the drug abuser swallows the lion share of family income because of buying drugs.

What are the Drugs?

Drugs are separated into two categories -

Soft drugs:

1. Alcohol
2. Cigarette
3. Marijuana
4. Glue, Hash etc

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Hard drugs:

1. Ecstasy
2. Speed
3. Amphetamine
4. Cocaine

Available drugs in Bangladesh:

▣ Opium;

1. Heroin
2. Pethedine
3. Cocaine

▣ Cannabis(Marijuana):

1. Ganja
2. Chorosh
3. Bhang
4. hashish

▣

Stimulant

1. Yaba(methamphetamine 30% and caffeine 70%)
2. Ectasy
3. Viagra(sildenafil)

▣ Sleeping pill:

1. Tranquilizer
2. Diazepam;

▣

Cough syrup

1. Phensidyl(codine, pseudoephedrine and chlorpheniramine)
2. Dexpotent

▣

G l u e

Drug addicted in percentage¹:

1. Male 93.9 %
2. Female (in Dhaka city) 20.6 %
3. Unmarried 64.8 %
4. Either students or unemployed (youth generation) 56.1 %
5. Smokers 95.4 %
6. Influenced by friends 85.7 %
7. Addicted to codeine-containing cough syrup 65.8 %
8. Addicted to more than one drug 64.3 %
9. Took drugs in groups 65.8 %
10. A history of unprotected sex 63.8 %.

Economical & Social impacts¹:

The average cost of drugs per person were from \$1.9 to \$3.1 per day or from \$707 to \$1135 per year. The economic impact of drug abuse included cost of drug itself, health care expenditure, lost productivity, and other impacts on society such as crimes and accidents. The patterns and cost of drug abuse were investigated among 996 drug abusers some were admitted to a drug dependence treatment centre in Dhaka,

Effects of these drugs in physical and mental health:**Phensidyl:**

Phensidyl is the combination of codeine, pseudoephedrine and chlorpheniramine.

Codeine: Common effects include drowsiness and constipation. Less common are euphoria, itching, nausea, vomiting, dry mouth, miosis, orthostatic hypotension, urinary retention, depression, and paradoxical coughing. Rare adverse effects include anaphylaxis, seizure, and respiratory depression².

Chronic use of codeine can cause physical dependence. When physical dependence has developed, withdrawal symptoms may occur if a person suddenly stops the medication. Withdrawal symptoms: drug craving, runny nose, yawning, sweating, insomnia, weakness, stomach cramps, nausea, vomiting, diarrhea, muscle spasms, chills, irritability, and pain. To minimize withdrawal symptoms, long-term users should gradually reduce their codeine medication under the supervision of a healthcare professional³.

Pseudoephedrine: CNS stimulation, insomnia, nervousness, excitability, dizziness and anxiety. Infrequent ADRs include: tachycardia and/or palpitations. Rarely, pseudoephedrine therapy may be associated with mydriasis (dilated pupils), hallucinations, arrhythmias, hypertension, seizures and ischemic colitis⁴; as well as severe skin reactions known as recurrent pseudo-scarlatina, systemic contact dermatitis, and nonpigmenting fixed drug eruption⁵. Pseudoephedrine, particularly when combined with other drugs including narcotics, may also play a role in the precipitation of episodes of paranoid psychosis⁶. It has also been reported that pseudoephedrine, amongst other sympathomimetic agents, may be associated with the occurrence of stroke⁷.

Chlorpheniramine: Potent anticholinergic agent, leading to the side-effects of dry mouth and throat, increased heart rate, pupil dilation, urinary retention, constipation, and, at high doses, hallucinations or delirium. Further side-effects include motor impairment (ataxia), flushed skin, blurred vision at nearpoint owing to lack of accommodation (cycloplegia), abnormal sensitivity to bright light (photophobia), difficulty concentrating, short-term memory loss, visual disturbances, irregular breathing, dizziness, irritability, itchy skin, confusion, decreased body temperature (in general, in the hands and/or feet), erectile dysfunction, excitability, and, although it can be used to treat nausea, higher doses may cause vomiting⁸. Some side-effects, such as twitching, may be delayed until the drowsiness begins to cease and the person is in more of an awakening mode.

Yaba:

Yaba is a combination of methamphetamine and caffeine.

Psychological effects of methamphetamine include euphoria, anxiety, increased libido, alertness, concentration, increased energy, increased self-esteem, self-confidence, sociability, irritability, aggressiveness, psychosomatic disorders, psychomotor agitation, dermatillomania (compulsive skin picking), hair pulling, delusions of grandiosity, hallucinations, excessive feelings of power and invincibility, repetitive and obsessive behaviors, paranoia, and - with chronic use and/or high doses - amphetamine psychosis^{9,10}.

Long term Methamphetamine use has a high association with depression and suicide as well as serious heart disease, amphetamine psychosis, anxiety, and violent behaviors. Methamphetamine also has a very high addiction risk.¹¹ Methamphetamine is not directly neurotoxic but long-term use can have neurotoxic side-effects. Its use is associated with an increased risk of Parkinson's disease due to the fact that uncontrolled dopamine release is neurotoxic^{12,13}. Long-term dopamine upregulation occurring as a result of Methamphetamine abuse can cause neurotoxicity, which is believed to be responsible for causing persisting cognitive deficits, such as memory loss, impaired attention, and decreased executive function. Similar to the neurotoxic effects on the dopamine system, methamphetamine can also result in neurotoxicity to the serotonin system¹⁴. Over 20% of people addicted to methamphetamine develop a long-lasting psychosis resembling schizophrenia after stopping methamphetamine. The condition persists for longer than 6 months and is often treatment resistant¹⁵.

Withdrawal symptoms of methamphetamine primarily consist of fatigue, depression, and increased appetite. Symptoms may last for days with occasional use and weeks or months with chronic use, with severity dependent on the length of time and the amount of methamphetamine used. Withdrawal symptoms may also include anxiety, irritability, headaches, agitation, restlessness, excessive sleeping, vivid or lucid dreams, deep REM sleep, and suicidal ideation¹⁶.

Caffeine overdose can result in a state of central nervous system over-stimulation called caffeine intoxication (DSM-IV 305.90)¹⁷, or colloquially the "caffeine jitters". The symptoms of caffeine intoxication are comparable to the symptoms of overdoses of other stimulants: they may include restlessness, fidgeting, anxiety, excitement, insomnia, flushing of the face, increased urination, gastrointestinal disturbance, muscle twitching, a rambling flow of thought and speech, irritability, irregular or rapid heart beat, and psychomotor agitation¹⁸. In cases of much larger overdoses, mania, depression, lapses in judgment, disorientation, disinhibition, delusions, hallucinations, or psychosis may occur, and rhabdomyolysis (breakdown of skeletal muscle tissue) can be provoked^{19,20}. Extreme overdose can result in death^{21,22}.

Withdrawal symptoms - including headache, irritability, inability to concentrate, drowsiness, insomnia, and pain in the stomach, upper body, and joints - may appear within 12 to 24 hours after discontinuation of caffeine intake, peak at roughly 48 hours, and usually last from 2 to 9 days²³.

Heroin:

In our country, heroin is mostly smoked within aluminum foil or cigarette paper, but in other countries this is injected.

Heroin causes constipation²⁴. Suppression of various cell-mediated immune pathways leading to opportunistic infections^{25,26,27}. Intravenous use with non-sterile needles and syringes or other related equipment may lead to transmission of infections like: HIV and hepatitis, the risk of contracting bacterial or fungal endocarditis. Physical dependence can result from prolonged use of all opioids, resulting in withdrawal symptoms on cessation of use. It decreases kidney function²⁸. Skin-popping more often results in abscesses, and direct injection more often leads to fatal overdose²⁹. A small percentage of heroin smokers, and occasionally IV users, may develop symptoms of toxic leukoencephalopathy^{30,31,32}. Symptoms include slurred speech and difficulty walking.

Pethidine:

Usual dose can cause nausea, vomiting, sedation, dizziness, diaphoresis, urinary retention and constipation. Over dosage can cause muscle flaccidity, respiratory depression, obtundedness, cold and clammy skin, hypotension and coma. Convulsive seizures sometimes observed in patients receiving parenteral pethidine on a chronic basis have been attributed to accumulation in plasma of the metabolite norpethidine (normeperidine). Fatalities have occurred following either oral or intravenous pethidine overdose^{33, 34}.

Alcohol:

Binge drinking:

In the USA, binge drinking is defined as consuming more than five units in men and four units in women. It increases chances for vandalism, fights, violent behaviours, injuries, drunk driving, trouble with police, negative health, social, economic, or legal consequences to occur³⁵. Binge drinking is also associated with neurocognitive deficits of frontal lobe processing and impaired working memory as well as delayed auditory and verbal memory deficits³⁵. Binge drinking combined with the stress of returning to work is a contributing factor to Monday deaths from heart attacks³⁶. The chances of becoming dependent are increased greatly in men who have 15 or more drinks each week or women who have 12 or more drinks each week. This is known as alcohol dependency³⁷.

Long-term effects of alcohol:

Individuals with an alcohol use disorder will often complain of difficulty with interpersonal relationships, problems at work or school, and legal problems; additionally patients do complain of irritability and insomnia. Alcohol abuse is also an important cause of chronic fatigue³⁸. Signs of alcohol abuse are related to alcohol's effects on organ systems. However, while these findings are often present, they are not necessary to make a diagnosis of alcohol abuse. Signs of alcohol abuse shows its drastic effects on the central nervous system acutely include inebriation and poor judgment; chronic anxiety, irritability, and insomnia. Alcohol's effects on the liver include elevated liver function tests (classically AST is at least twice as high as ALT). Prolonged use leads to cirrhosis and failure of the liver. With cirrhosis, patients develop an inability to process hormones and toxins. The skin of a patient with alcoholic cirrhosis can feature cherry angiomas, palmar erythema and - in fulminant liver failure - jaundice and ascities. The derangements of the endocrine system lead to gynecomastia. Inability to process toxins leads to hepatic encephalopathy.

Binge drinking is associated with individuals reporting fair to poor health compared to non-binge drinking individuals and which may progressively worsen over time. Alcohol also causes impairment in a person's critical thinking. Person's ability to reason in stressful situation is compromised, and they seem very inattentive to what is going on around them³⁵. Social skills are significantly impaired in people suffering from alcoholism due to the neurotoxic effects of alcohol on the brain, especially the prefrontal cortex area of the brain. The social skills that are impaired by alcohol abuse include impairments in perceiving facial emotions, prosody perception problems and theory of mind deficits; the ability to understand humour is also impaired in alcohol abusers³⁹. Patients who abuse alcohol are less likely to survive critical illness. Research conducted at Ohio State University Medical Center found that patients who suffer from alcoholism or alcohol withdrawal are at a much higher risk for having sepsis and were more likely to die during hospitalization⁴⁰.

Alcohol abuse causes neuroinflammation and leads to myelin disruptions and white matter loss; the developing adolescent brain is at increased risk of brain damage and other long lasting alterations to the brain⁴¹. Adolescents with an alcohol use disorder damage the hippocampal, prefrontal cortex, and temporal lobes⁴². Children aged 16 and under who consume alcohol heavily display symptoms of conduct disorder. Its symptoms include troublesome behaviour in school, constantly lying, learning disabilities and social impairment⁴³.

Cannabis:

Acute adverse effects: ⁴⁴

- Anxiety and panic, especially in naive users
- Psychotic symptoms (at high doses)

Chronic adverse effects: ⁴⁴

- Cannabis dependence syndrome (in around one in ten users)
- Chronic bronchitis and impaired respiratory function in regular smokers
- Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders
- Impaired educational attainment in adolescents who are regular users
- Subtle cognitive impairment in those who are daily users for 10 years or more

Possible adverse effects of regular cannabis use with unknown causal relation: ⁴⁴

- Respiratory cancers
- Behavioural disorders in children whose mothers used cannabis while pregnant
- Depressive disorders, mania, and suicide
- Use of other illicit drugs by adolescents

Drug addiction brings on rapid erosion of educational and cultural, moral and family values. The addicts lose their professional and educational capabilities, self-dignity, and get involved in serious or petty criminal activities. The sole aim in life of an addict becomes the procurement and use of drugs.

Time is ripe for leaders at the highest level to wake up to the danger posed to healthy existence of society as more and more new addicts join the ranks of the hardcore ones. This slide must be arrested at all costs. The Drugs and Narcotics Department was created nearly two decades ago, especially to counter the production and availability of addictive drugs. But it has done little over the years to attain its given objectives. The corruption, allegedly, runs high in it.

Political commitment is required to combat the illicit drug-traffickers who are sucking the blood of innocent youths and becoming rich very quickly through smuggling of drug.

Preventive education against drug abuse is essential. Enforcement of laws by the law enforcing agency is needed to curb drug trafficking. The whole community should participate in awareness raising program and peer-counseling is important to change the negative behavior of the youth. If we fail to control of this problem it will destroy the whole civilization.

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Drug Abuse and Cardiac Problem

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Abstract

Drug abuse has reached epidemic proportions in many countries including Bangladesh and threatens to overwhelm economic, social, and health care systems. In addition to their effects on the central nervous system, many of these agents induce profound changes in the heart and circulation that are responsible for a significant proportion of drug-related morbidity. Drugs that can affect the cardiovascular system are cocaine, heroin, inhalants, ketamine, lysergic acid diethylamide (LSD), marijuana, 3,4-methylenedioxymethamphetamine (MDMA), methamphetamine, nicotine, phencyclidine (PCP), prescription stimulants, steroids. This article reviews the cardiovascular problems associated with drug abuse.

Introduction

Humans have used drugs of one sort or another for thousands of years. Wine was used at least from the time of the early Egyptians; narcotics from 4000 B.C.; and medicinal use of marijuana has been dated to 2737 B.C. in China. The abuse of drugs is common and it is inevitable that doctors will have to manage and treat their associated ill effects. Abused drugs are complex and can induce profound changes in cardiovascular function, both acute and chronic. Abused drugs are often taken together, which can result in complex synergistic interactions with potentially detrimental effects. A high index of suspicion with early intervention and management is often the key to successful treatment.

Cannabis

Epidemiological data indicate that cannabis users are significantly more likely to experience palpitations with the majority being dose related sinus tachycardia^{1,2}. Cannabis has a biphasic effect on the autonomic nervous system, depending on the dose absorbed³. Low or moderate doses can increase sympathetic and reduce parasympathetic activity, producing a tachycardia and an increase in cardiac output. In contrast, higher doses inhibit sympathetic and increase parasympathetic activity, resulting in bradycardia and hypotension.

Reversible ECG abnormalities affecting the P and T waves and the ST segment have been reported⁴. Supraventricular and ventricular ectopic activity can occur. In patients with ischemic heart disease, cannabis increases the frequency of anginal symptoms at low levels of exercise. This occurs as a result of a drug-induced increase in heart rate and myocardial contractility that increases myocardial oxygen demand⁵ and a reduction in the oxygen carrying capacity of blood due to the formation of carboxyhaemoglobin⁶. These adverse haemodynamic changes may trigger plaque rupture in vulnerable individuals culminating in myocardial infarction⁶ and sudden cardiovascular death⁷. Myocardial infarction has also been reported in the presence of normal coronary arteries, suggesting coronary vasospasm⁷. Other reported cardiovascular effects associated with cannabis consumption include transient ischaemic attacks and strokes⁷.

Cannabis may often be used in combination with other recreational drugs such as cocaine and amphetamines, which may have synergistic cardiovascular effects^{8,9}.

Narcotic analgesics

Morphine, pethidine and heroin are the most commonly used narcotic drugs by drug addicts. Narcotic agents act centrally on the vasomotor center to increase parasympathetic and reduce sympathetic activity¹⁰.

These autonomic changes, combined with histamine release from mast cell degranulation, can result in bradycardia and hypotension. Cardiac arrhythmias-including premature atrial and ventricular ectopic activity, atrial fibrillation, idioventricular rhythm, and ventricular tachyarrhythmias-have all been reported⁵. Bacterial endocarditis, affecting mainly right-sided cardiac structures, is a well-known complication of intravenous narcotic drug abuse, and it is sometimes associated with pulmonary abscesses. Heroin overdose can cause noncardiogenic pulmonary edema, the onset of which can be delayed for up to 24 hours after admission¹¹. A disruption in alveolar-capillary membrane integrity has been suggested as a mechanism.

Cocaine, amphetamine, and ecstasy (MDMA)

Cocaine, amphetamine, and ecstasy all share similar adverse effects on the cardiovascular system, related predominantly to sympathetic nervous system activation. Cocaine and its free-base form crack act by inhibiting the re-uptake of norepinephrine and dopamine at sympathetic nerve terminals.

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Circulating catecholamine concentrations can be elevated as much as 5-fold in cocaine users¹². At high doses, cocaine can impair myocyte electrical conduction and contractility¹².

Amphetamine and its derivative ecstasy produce indirect sympathetic activation by releasing norepinephrine, dopamine, and serotonin from central and autonomic nervous system terminals.

Blood pressure changes

The high levels of circulating catecholamines and sympathetic activation commonly cause hypertension. However, hypotension can also occur⁵.

Myocardial ischemia and infarction

Cocaine and amphetamine can cause myocardial ischemia and infarction in patients with or without coronary artery disease. The mechanism is uncertain, but may be related to the elevated catecholamine concentration, which increases myocardial oxygen demand, coronary artery spasm, platelet aggregation, and thrombus formation^{3,5,13}. Cocaine can produce a procoagulant effect by decreasing concentrations of protein C and antithrombin 3 and potentiating thromboxane production⁵.

Long-term use of cocaine and amphetamine can cause repetitive episodes of coronary spasm and paroxysms of hypertension, which may result in endothelial damage, coronary artery dissection, and acceleration of atherosclerosis.

Aortic dissection, valvular damage, and endocarditis

Paroxysmal increases in blood pressure can lead to aortic dissection or valvular damage that increases the risk of endocarditis affecting mainly left-sided cardiac structures¹². Endocarditis is often associated with unusual organisms such as *Candida*, *Pseudomonas*, or *Klebsiella* and frequently has an aggressive clinical course with marked valvular destruction, abscess formation, and a need for surgical intervention.

Cardiomyopathy

Prolonged administration of cocaine or amphetamines can also lead to a dilated cardiomyopathy⁵. Etiologic mechanisms include repeated episodes of subendocardial ischemia and fibrosis and myocyte necrosis produced by exposure to excessive catecholamine concentrations, infectious agents, and heavy metal contaminants (manganese is present in some cocaine preparations).

Pulmonary edema and pulmonary hypertension

Noncardiogenic pulmonary edema and pulmonary hypertension can also occur with cocaine and amphetamine misuse, although the precise underlying mechanism remains unknown¹⁰.

Arrhythmias

The adverse cardiovascular changes and sympathetic stimulation associated with cocaine and amphetamine ingestion predispose to myocardial electrical instability, precipitating a wide and unpredictable range of supraventricular and ventricular tachyarrhythmias. The presence of fibrotic scars, myocardial ischemia, and left ventricular hypertrophy can act as a substrate for arrhythmogenesis. Cocaine possesses class¹ antiarrhythmic properties (blocks sodium channels) and can impair cardiac conduction causing prolongation of the PR interval, QRS complex, and QT interval. Cocaine can also cause a wide range of bradyarrhythmias, including sinus arrest and atrioventricular block¹⁰.

Lysergic acid diethylamide (LSD) and psilocybin ("magic mushrooms")

Lysergic acid diethylamide (LSD) and psilocybin are commonly used hallucinogenic agents that are structurally related and have similar physiologic, pharmacologic, and clinical effects. LSD is about 100 times more potent than psilocybin. Their mechanisms of action are complex with various agonist, partial agonist, and antagonist effects at serotonergic, dopaminergic, and adrenergic receptors⁵.

The adrenergic effects of these drugs are usually mild and can give rise to general sympathetic arousal leading to dilated pupils, tachycardia, hypertension, and hyperreflexia. Although cardiovascular complications are rarely serious, supraventricular tachyarrhythmias and myocardial infarction have been reported¹⁴. Changes in serotonin-induced platelet aggregation and sympathetically induced arterial vasospasm may have been contributory factors leading to the onset of myocardial infarction¹⁴.

Volatile substance abuse

The abuse of volatile substances is an increasing problem among young male adolescents. The products used are legal, cheap, and easily available. Following inhalation, feelings of euphoria, excitement, and invulnerability can occur rapidly, but are short-lived¹⁰.

Cardiac arrhythmias are presumed to be the main cause of death from volatile substance abuse. Volatile substances may induce supraventricular or ventricular tachyarrhythmias by sympathetic activation or by myocardial sensitization to circulating catecholamines¹⁵. Some abusers spray the substances directly into the mouth, which can result in intense vagal stimulation and a reflex bradycardia. Profound bradycardia can evolve into asystole or secondary ventricular tachyarrhythmias. Some volatile compounds can reduce sinoatrial node automaticity, prolong the PR interval, and induce atrioventricular block⁵. Myocardial ischemia and infarction have been reported and are believed to be caused by a combination of coronary vasospasm, hypoxia caused by

the formation of carboxyhemoglobin or methemoglobinemia, or excessive sympathetic stimulation⁵. Long-term misuse can induce a poorly characterized cardiomyopathy¹⁶.

The abuse of illegal drugs is endemic in society and has the potential to cause major acute changes in cardiovascular function and irreversible damage to the heart. These drugs are frequently taken together as "cocktails," often in conjunction with alcohol. These combinations can have complex synergistic interactions, with potentially detrimental effects.

Many patients who present with complications will be unable or unwilling to provide a history of illegal drug use. Recreational drug use should always be suspected and looked for in patients presenting with unexplained or unusual cardiovascular disturbances associated with mood disturbances or central nervous system dysfunction. As drug misuse continues to permeate every level of society, it is inevitable that physicians will have to manage the devastating complications of these compounds. An awareness of the life-threatening cardiovascular effects, along with early diagnosis and intervention, is often the key to successful treatment.

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Case Report

Acute Intermittent Porphyria: A Rare Inborn Error of Haem Metabolism

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A b s t r a c t

A 22 year young boy presented with recurrent abdominal pain, generalized weakness & wasting with hypertension in Medicine ward CMCH. Subsequently he was diagnosed as a case of Acute Intermittent Porphyria (AIP). Though not common, any patient with unexplained abdominal crisis specially young with any peripheral or central nervous system dysfunction should raise the clinician's suspicion of being porphyric patient as prompt management can relieve the patient from progressive neurological damage and disability.

I n t r o d u c t i o n

Porphyrias are disorder of haem biosynthetic pathway. The one with most serious consequences is acute intermittent porphyria (AIP), inherited as an autosomal dominant disease, remains clinically silent in the majority of the population who carry the trait. Presentation is in early adult life usually around the age of 30yrs and women are more affected than male. The disease is wide spread but specially common in Scandinavia & Great Britain. The disorder is caused by partial deficiency of porphobilinogen deaminase enzyme, leading to increased excretion of Amino Laevulanic Acid (ALA) and Porphobilinogen (PBG) in the urine^{1,6}.

The presentation is with acute relapsing and remitting neurological syndrome, invariably with acute abdominal pain and features of autonomic dysfunction such as tachycardia, hypertension, and constipation. Other frequent association includes neuropsychiatric manifestations like depression, anxiety, psychosis, convulsion. Often there is profound hyponatraemia due to inappropriate ADH release. Neuropathy is predominantly motor (70%) & can lead to quadriplegia with respiratory muscle paralysis. Cranial & sensory nerves may be affected. Skin is never affected like other photosensitive porphyria.

There is no proven explanation for the episodic pattern of these attacks. However they are often provoked by drugs, diet, alcohol and even fasting. In a significant number of cases no precipitant can be identified^{2,4}.

The diagnosis can be confirmed by demonstrating an increased amount of PBG in the urine during an attack. Freshly voided urine is of normal colour but it may turn dark upon standing in light and air. All family members should be screened to detect latent cases^{3,1}. Treatment with a high carbohydrate diet diminishes the number of attack in some patients. Acute attacks may be life threatening and require prompt diagnosis and withdrawal of the inciting agent and treatment with narcotic analgesic and intravenous high conc. glucose and haem arginate which inhibit ALA synthase activity and thus reduce ALA and PBG level. The intravenous dose of haem is up to 4mg/kg twice daily for four days keeping in mind about adverse consequences specially phlebitis & coagulopathy. Recovery from severe motor neuropathy may require long time even years. Liver transplantation is an option for patients with disease poorly controlled by medical therapy^{1,2}.

Case Report: A 22 year old canteen boy, hailing from Chittagong City, admitted in Medicine ward CMCH, on 16-09-2007 with the complaints of episodic attack of severe abdominal pain for the last 3 years, associated with generalized weakness, wasting and walking difficulties for the same duration. Patient elaborated that pain was diffuse, not associated with fever or vomiting but aggravated by fasting and unrelieved by antacids. He had no preceding NSAID intake history, or any history of previous jaundice, diabetes or hypertension. He admitted for several times during relapse of pain but the diagnosis was inconclusive though he improved after symptomatic treatment. There was no history of trauma, sexual exposure, contact with chemicals or alcohol abuse. He had no bladder or bowel difficulty except constipation during attack. His appetite was good and he was not suffering from any respiratory or cardiac disease. No family member was suffering from such illness. On examination, patient was found conscious ill looking, malnourished, mourning with pain, dehydrated, non anaemic & non icteric. No cyanosis, clubbing or pigmentation was found. His temperature was 99F, RR 16/minute, no enlarged lymph node found. Thyroid gland was normal, Pulse 140/m, regular & BP 170/100 mmHg in supine position and 140/90 mmHg in standing position. Bed side urine colour was normal on fresh sample but later on it became red-tea colour (Figure 1).

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Figure 1: The patient of acute intermittent porphyria with peripheral neuropathy evidenced by wrist and foot drop. There is sample of freshly voided urine of normal colour (left side) and dark reddish urine (right side) after exposure to sun light.

Abdominal examination showed diffuse tenderness on deep palpation but no hepatosplenomegaly, ascitis or visible veins was found. Hernial orifices were intact. Genitourinary system examination revealed no abnormality. On neurological examination higher cerebral function was found normal, no cranial nerve palsy was seen. Wasting of muscles of both upper and lower limbs was present with hypotonia. Muscle power diminished in both limbs (3/5) in all groups. Superficial reflexes were present but deep reflexes were diminished in both upper and lower limbs, more marked distally. Planter reflexes were flexor, gait was high stepping, no tremor or involuntary movement was present. No sensory abnormality was detected; vibration and joint position sense were normal, Romberg's sign was negative. No peripheral nerve thickening or no sign of meningeal irritation found. From history and clinical examination we suspected the patient suffering from porphyric neuropathy and investigated to establish the case as well as excluding other possibilities.

The laboratory profile was as follows:

Hb% 11 gm/dl ESR 15 mm in 1st hr. TC $8.5 \times 10^9/L$. Platelet 220 $\times 10^9/L$. Urine R/E: Sugar-Nil. Albumin-Nil, Pus cell - 0-2/HPF RBC Nil. RBS: 85 mg/dl, PBF: Eosinophilia.

Serum Na⁺ 128 mmo1/L, creatinine 0.7mg/dl

Bilirubin 0.3mgI/L, HBsAg-Ve. SGPT 89 UL, Serum amylase 79 U/L.

TSH: 2.51 mU/L, VDRL: Non reactive

X ray chest P/A Clear, ECG Sinus Tachycardia. Plain X-ray Abdomen. A/P normal

USG Whole Abdomen, Endoscopy of upper GIT and Echocardiography- normal

Slit skin smear from ear & forehead: negative for mycobacterium lapre.

NCV: Motor poly neuropathy

Urine for porphobilinogen: PBG Positive

Thus the diagnosis was established as a case of an acute intermittent porphyria.

The Patient had a stormy course in hospital with recurrent severe colicky abdominal pain which was controlled by intravenous opioid analgesics. Dehydration and hyponatremia were corrected by 5% Dextrose Saline infusion. There was labile hypertension and tachycardia which was controlled by propranolol. 25% glucose infusion & plenty oral glucose rich fluid intake helped in subsiding episodes of severe pain. The patient was discharged after a period of 20 days hospital stay. He was given chart of harmful drugs that may precipitate the condition. During discharge his condition was stable, neurological deficit was significantly improved and hypertension was controlled. His family members were advised to screen for urine porphobilinogen in the specialized centre.

Discussion

An acute attack of AIP varies considerably in its clinical presentation and patients may be referred to an internist, surgeon, neurologist, psychiatrist or gynaecologist. A high level of clinical suspicion is necessary in order not to miss the diagnosis which is based on relatively simple laboratory examination for porphobilinogen. An increased urinary excretion of porphobilinogen in the absence of lead poisoning points towards a diagnosis of acute intermittent porphyria. Our patients did not have any history of contact with lead substances. Moreover no clinical feature of lead poisoning like bluish discoloration of gums due to lead sulfide deposition (Burton's line) or Basophilic stippling in red blood cells was absent^{4,5}.

A brief review of the haeme biosynthetic pathway is outlined in order to explain the fundamental defect in AIP (Figure 2).

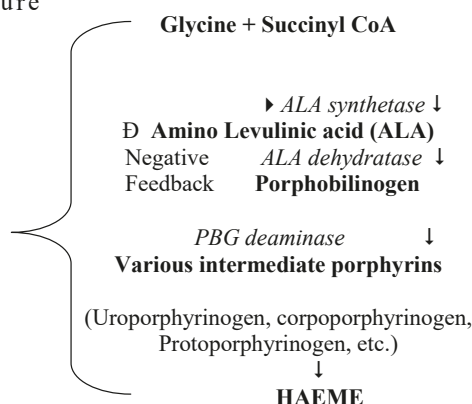


Figure 2 : Biosynthetic Pathway of haem

ALA synthetase is the first and also the rate limiting enzyme in the pathway. In AIP there is reduction in the enzyme PBG deaminase, resulting in diminished haem synthesis causes induction of the rate limiting enzyme ALA synthetase via a bio feedback mechanism and thus results in high level porphobilinogen (PBG) in the blood and urine. PBG is generally so strikingly increased during an attack of AIP, quantitative event on spot sample rather than a 24 hour collection of urine is highly informative. During collection of urine a dark plastic jug should be used to protect the sample from light as porphyrin are fluorescent substances which on exposure to light and air oxidize and turn intensely reddish. During shipping it is stored in a refrigerator or in an ice chest^{1,4}.

The diagnosis of AIP is always an important item of medical information even when there is no symptom. It may influence the choice of drugs to treat other medical conditions, surgery and anesthesia. Some drugs are potentially dangerous like sulphonamide, Tranquilizers and sedative, Griseofulvin, Carbamazepine, Phenyton, Valproate, OCP, Alcohol, Rifampicin, Tetracycline, Diclofenac. Some drugs are probably safe like Narcotic analgesic, Aspirin, Acetaminophen, Chlorpromazine, Penicillin, streptomycin, Glucocorticoid, Insulin, Atrophin, SSRI etc. If a question of drug safety arises a physician or medical centre specialized in porphyria should be conducted^{6,8}.

Acute attacks require a prompt diagnosis, withdrawal of the inciting agent, and treatment with narcotic analgesics, intravenous glucose and haematin. Electrolyte imbalances requires careful monitoring and correction. Treatment with a high carbohydrate diet diminishes the number of attack in some patients. A minimum of 300gm/day of carbohydrate should be provided orally or intravenously. Haeme products like haeme arginate, is the recommended specific therapy for AIP and should be started as early as possible; the administration of this end-product of the haeme biosynthesis pathway improves the underlying biochemical disturbance by reducing porphyrin precursor excretion. Adverse effects commonly seen are phlebitis and coagulopathy. This costly drug is not routinely available in our country. So management strategies for this rare disease should be planned to relieve symptoms, prevent inciting factor, avoiding harmful drugs and taking plenty glucose rich fluids regularly in our perspective^{1,2,7}.

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Peripartum Cardiomyopathy

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A b s t r a c t

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy that presents with heart failure secondary to left ventricular systolic dysfunction. Onset is from the last trimester of pregnancy to 5 months postpartum. Diagnosis in the last trimester is complicated by the fact that the early symptoms of this disorder may mimic the symptoms of normal pregnancy. However, it is essential for the practitioner dealing with such population to have a high degree of clinical suspicion for early diagnosis and management. Echocardiography is used to diagnose this entity and monitor the therapy. We present a case report of a 40-year-old woman who presented two days post-partum with respiratory distress and early echocardiography helped in diagnosing PPCM. The aim of this report is to make health professionals aware of the possibilities of PPCM in a woman with dyspnoea in the postpartum period.

Keywords: *Peripartum cardiomyopathy, Left ventricular dysfunction, Echocardiography.*

I n t r o d u c t i o n

Peripartum cardiomyopathy (PPCM) is an uncommon type of heart failure of unknown cause occurring late in pregnancy or in the postpartum period. Although PPCM is associated with high morbidity and mortality it is often undetected or misdiagnosed because of its low incidence and nonspecific symptoms. Additionally, pregnancy-related diseases may have similar clinical presentations. Unfortunately, PPCM is a disease whose underlying etiology and natural history remain incompletely understood.

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Risk Symptoms of PPCM, which include fatigue, edema, and dyspnea, are similar to those for the normal spectrum of peripartum states and pregnancy comorbidities such as pulmonary emboli. This article reviews the etiology, clinical symptoms, treatment, and prognosis for PPCM, which must be understood to provide patients with the most efficient and appropriate care.

Case Report

A 40 years old woman came to the emergency department with sudden onset of dyspnoea two days after giving birth of her first child by normal vaginal delivery. She denied any chest pain or calf pain. Her medical history was uneventful, except for flulike symptoms approximately one month before childbirth that included coughing, nausea, vomiting, and diarrhea. In the emergency department, the patient appeared to be slightly anxious. She had a blood pressure of 140/80 mm Hg, a pulse rate of 110 beats per minute, a respiratory rate of 22 breaths per minute, and an oxygen saturation of 93% on room air. Physical examination showed S3 heart sound, bilateral basal crackles both lungs but no jugular venous distention, edema, or hepatosplenomegaly. She was slightly tachypnoeic but not in any acute respiratory stress. Laboratory tests revealed no proteinuria and a BNP level of 1250 pg/mL. ECG showed a sinus tachycardia, rate 110 beats per minute. Chest radiograph findings were noted to cardiomegaly with mild pulmonary congestion (Figure 1).

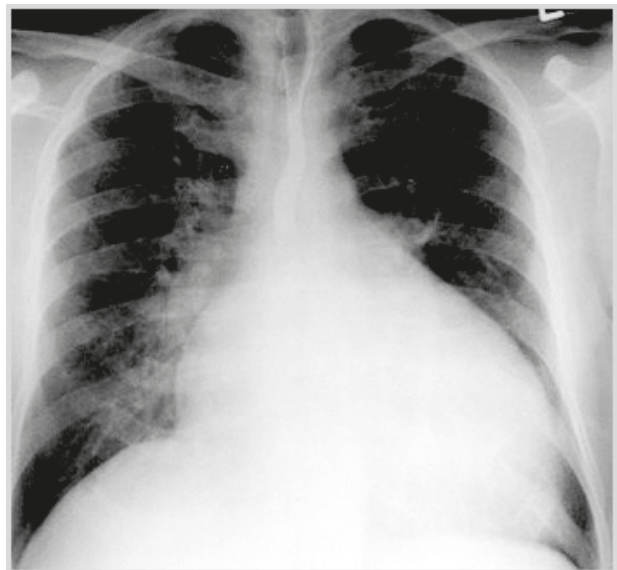


Figure-1: Chest X-ray P/A view

A CT scan of the chest was done which was negative for pulmonary emboli. An echocardiogram was done at that time which showed left atrial and LV dilation, global LV hypokinesia, and an estimated ejection fraction of 30% to 35% & Grade 1+ MR (Figure-2). The patient was given appropriate medications for heart failure, which alleviated her symptoms. Her follow-up echocardiogram three months later showed normalization of her ejection fraction to

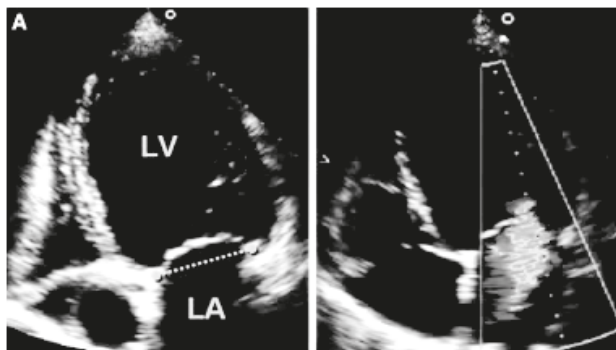


Figure-2: TTE, parasternal long-axis view: LV = left ventricle; LA = left atrial.

Discussion

Heart failure associated with pregnancy was first observed and recorded as early as the 19th century by Ritchie and Virchow. Adapted from work by Demakis et al.¹. The exact incidence of PPCM is unknown but is estimated to be 1 in 3000-4000 deliveries in the United States². Specific data is rare because mild forms are often unrecognized. PPCM constitutes less than 1% of all cardiovascular events related to pregnancy³. Risk factors classically identified in the literature include black race, increase age (>30 years), multiparity, twin pregnancy, pre eclampsia and gestational hypertension^{1,4}.

Despite many hypotheses, the cause and mechanism of pathogenesis of PPCM remain unknown. Early investigations proposed myocarditis as the cause for PPCM where anti-inflammatory treatment resulted in clinical improvement⁵. Further studies failed to establish this causal link between myocarditis and development of PPCM^{6,7}. Additionally, Felker et al. confirmed that the absence or presence of inflammation on endomyocardial biopsy tissue did not predict outcome in patients with PPCM⁸.

Persistent viral antigen has been also postulated as a trigger for the development of PPCM. Presence of viral genomic material, including enterovirus (coxsackie virus), parvovirus B19, adenovirus and hepatitis virus was isolated in biopsy material of patients with idiopathic dilated cardiomyopathy. Further, the authors demonstrated an association between clinical improvement of left ventricular systolic function and viral clearing⁹. Despite these promising findings, further studies are needed to clearly identify virus infection as the cause for development of PPCM. Many animal and clinical investigations support to the hypothesis that immune activation, dysregulation of cellular apoptosis pathways and

upregulated humoral immunity contribute to the pathogenesis of PPCM. Whereas the importance of raised high sensitivity c-reactive protein in plasma of patients with new and evolving PPCM merits additional evaluation, concentrations of the inflammatory cytokine TNF-alpha, elevated immunoglobulins against cardiac myosin as well as markers of apoptosis (Fas/Apo-1) are well correlated with left ventricular function and mortality. Additionally, animal data suggest that the cardiac myocyte-specific STAT3 pathway is necessary for protection of the heart from postpartum stress¹⁰. Taken all available data together, so far no cause has been clearly identified for the development of PPCM.

The clinical presentation of patients of PPCM is similar to that of other forms of left ventricular systolic failure. Clinical symptoms are dyspnea, cough, chest pain, and orthopnea. Additionally physical examination may reveal signs such as tachycardia, hypertension, ventricular gallop rhythm, mitral regurgitation murmur, hepatosplenomegaly, ascites, or jugular venous distension. Ancillary studies include electrocardiogram (ECG), chest radiograph, Doppler-echocardiography and possibly thoracic CT-scan. To recapitulate, proper medical history and an accurate physical examination combined with routine ancillary studies may ensure the diagnosis of PPCM. Clinicians should think of PPCM in any peripartum patient with unexplained disease.

Medical therapy of PPCM is similar to that for others forms of congestive heart failure. Thus digoxin, angiotensin-converting enzyme (ACE) inhibitors, diuretics, sodium restriction and after-load reducing agents are the mainstays of medical therapy¹¹⁻¹³. If necessary, catecholamines like dopamine and dobutamine can be given. Arrhythmia treatment should be performed using standard guidelines and protocols. Low molecular weight heparin prophylaxis is routinely advised. Immunosuppressive therapy may be indicated when peripartum myocarditis and cardiomyopathy is present⁵. Intra-aortic balloon pumping or insertion of a left ventricular (LVAD) or biventricular assist device (BVAD) should be considered if the patient is not responding to medical management. As a last resort heart transplantation can be considered for non responders.

Peripartum cardiomyopathy is an uncommon complication of pregnancy with unknown cause and potentially life-threatening complications. Once the diagnosis is confirmed treatment of PPCM does not differ from that of other dilated cardiomyopathies. Echocardiography appears to be extremely valuable in diagnosing PPCM, formulating prognosis of recovery and following the course of the disease. Especially ejection fraction and left ventricular end diastolic dimensions at the time of diagnosis may be predictive of long-term cardiac dysfunction. Currently, there is no consensus regarding recommendations for future pregnancy after PPCM. Nevertheless the risk of developing PPCM, with future pregnancies, remains high. Particularly in the presence of persistent left ventricular dysfunction, a subsequent pregnancy should be discouraged and avoided¹⁴.

Prognosis in the United States is variable with a maternal mortality of 25 to 50 percent¹⁴. However outcome differs widely between reports. Death is generally attributed to arrhythmia or thrombo-embolism. If congestive cardiomyopathy persists after 6 months it is likely irreversible and portends decreased survival.

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Oral Histoplasmosis with Previously Treated Pulmonary Tuberculosis: A Case Report

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Abstract

Oral Histoplasmosis is a deep fungal infection may present as oral ulceration and can be confused with oral mucosal malignancies, tuberculosis and other fungal diseases. It mostly affects individual having immunodeficiencies like tuberculosis and AIDS, but may also affect immunocompetent individuals. Here we presented a case of oral histoplasmosis with previously treated pulmonary tuberculosis and was treated by oral itraconazole. Complete disappearance of oral ulceration was evident following four weeks treatment and the patient is in regular follow up with maintenance therapy for last ten months.

Keywords: Itraconazole, Oral Histoplasmosis, Oral Ulcer, Tuberculosis.

Introduction

Histoplasmosis is caused by *Histoplasma capsulatum*, a dimorphic pathogenic fungus that develops a branching hyphal form in soil and a yeast form in the host tissue¹. Infection by this organism is endemic in North America, Central America and South America, but it also has been reported in Africa, Asia, India and Australia². The infective agents are airborne spores from the mycelial form. In Bangladesh, sporadic cases have been reported in different literature³⁻⁶. The inhalation of spores, which are present in chicken, pigeon and bat excrement, by immunocompetent hosts usually results in an asymptomatic pulmonary infection.

Hosts with immunosuppression may develop a generalized infection that involves several organs⁷. Clinically the disease is manifested as weakness, fever, weight loss, mucocutaneous lesions and hepatosplenomegaly.

Clinically Histoplasmosis is classified into primary acute pulmonary form, chronic pulmonary form and disseminated form (DH). The course of this disease can be affected by the immune status of the host and by the degree of exposure to infective propagules⁸. Oral lesions have been reported in 25 to 45 percent of patients with documented cases of progressive disseminated histoplasmosis and in several case reports⁹.

Around 30-66% of patients with DH have oral lesions, frequently presenting as the initial sign. Generally lesions of histoplasmosis in the oral cavity are the local manifestation of pulmonary or disseminated disease¹⁰ but rarely may they be the primary or even the only manifestation of the disease¹¹.

H. capsulatum is a major opportunistic pathogen in patients infected with the human immunodeficiency virus (HIV) in endemic areas; approximately 5 percent of patients with AIDS in these areas develop disseminated histoplasmosis¹². In immunocompetent hosts, few cases of oral histoplasmosis without detectable systemic involvement have been described. Oral histoplasmosis may manifest at any region of the mouth as nodules, deep ulcerative or vegetative lesions or painful shallow lesions¹³.

Diagnosis of Histoplasmosis is usually based on clinical signs and symptoms, organ function tests and fungal demonstration or culture from a lesion or secretion. Serological testing may help together with other suggestive but non-diagnostic clinical criteria^{14,15}. Recently, molecular typing of *H. capsulatum* has been shown to be useful in distinguishing relapse from reinfection, and in defining the likely source of the infection¹⁶. Furthermore, molecular typing of *H. capsulatum* by the random amplified polymorphic DNA polymerase chain reaction (RAPD-PCR) method is able to discriminate among clinical isolates, making it a useful tool for epidemiological investigation¹⁶.

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Amphotericin B has been the drug of choice for systemic histoplasmosis^{17,18}. The options have broadened considerably since the introduction of the azole compounds, ketoconazole and itraconazole^{14, 17}. The successfully treated 1st reported case in Bangladesh was in 1982³.

Case Report

A 65-year-old male farmer presented with two painful ulcers on upper alveolar gingivae and palatal mucosae and poor general health for three weeks. There was a history of difficulty in mastication with no history of pus discharge, paresthesia or numbness. Patient was habituated with smoking and gave no history of extra-marital sexual exposure. He gave history of previous pulmonary tuberculosis with irregular treatment. The other medical histories of patient were noncontributory. Extraoral examination revealed imaciated face with mild anaemia and enlarged, firm, non-tender, non-fixed lymph nodes in bilateral submandibular regions. Intraoral examination revealed poor oral hygiene with two almost identical ulcers in maxillary alveolar ridge and palatal mucosae on both sides. The indurated ulcers were tender with edematous, raised margin and the surfaces were covered with slough and focal areas of necrosis (Figure 1).



Figure 1: Ulcer present on the palatal mucosa and gingiva

Haematological values were within normal limits with normal blood sugar level and non-reactive VDRL, HIV1 and HIV2 in Western blot assay. Orthopantomogram showed no significant alveolar bone loss. Chest radiograph shows Koch's Lesion (Bilat) with volume reduction (Figure 2). Considering the possibilities of deep fungal infection, tuberculosis or mucosal malignancies, incision biopsy was done. Initial biopsy report revealed severely inflamed and oedematous fibrocollagenous tissue covered by ulcerated stratified squamous epithelium showing minor salivary glands with multiple granulomata composed of epitheloid cells with extensive areas of caseation necrosis which was consistent with tuberculosis. The patient was re-evaluated by a group of physicians who recommended repeat biopsy which revealed dense infiltration of acute and chronic inflammatory cells including many eosinophils, aggregates of epitheloid histiocytes and

some of the histiocytes contained intra-cytoplasmic round to oval bodies; morphologically consistent with histoplasmosis. There was no evidence of caseous necrosis or malignancy in the tissue sections (Figure 3). Based on the clinical features and investigatory findings, a final diagnosis of oral histoplasmosis in a non-HIV patient was made. Then the patient was evaluated systemically, where systemic involvement of histoplasmosis was ruled out.

With proper education and counseling, patient was treated with oral Itraconazole 200 mg twice daily. The lesions completely healed following four weeks medication (Figure 4). The patient, however, is under regular follow-up and no recurrence is noted after ten months.



Figure 2: Chest radiograph shows Koch's Lesion

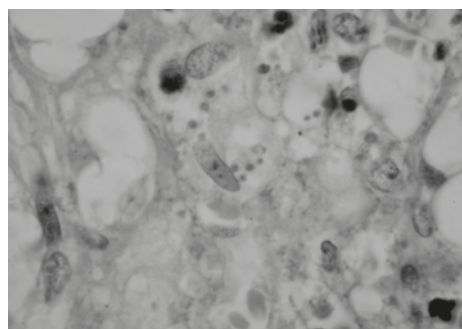


Figure 3: Histopathology shows epitheloid histiocytes with intracytoplasmic round to oval bodies.



Figure 4: Post treatment showing complete resolution of palatal lesion

Discussion

H. capsulatum is the organism responsible for occurring the fungal infection, Histoplasmosis. Oral manifestations, usually associated with the chronic disseminated form of the disease, constitute a rare event in immunocompetent patients. Most primary infections are asymptomatic, or the symptoms are acute and affect only the lungs. Oral lesions show a varied clinical appearance and are rarely painful. Mostly they presented as an ulcerative lesion with an elevated border, located mainly on the gingiva, tongue and palate. The reported case presented with painful ulcer in gingiva and palatal mucosa with dysphagia and poor general health.

Oral lesions of histoplasmosis occurred only as secondary local manifestations of pulmonary or disseminated disease⁹. Some investigators have claimed that primary oral histoplasmosis is possible and may develop as a result of direct inoculation of the fungus into the mucosa. Our reported case did not present any pulmonary infection or disease involvement. Clinicians usually diagnose primary oral histoplasmosis after discovering the lesions in the upper digestive tract in the absence of pulmonary signs and the diagnosis is based on identification of the fungus. For superficial and accessible oral lesions, cytologic evaluation and a biopsy usually are recommended. However, in cases in which the lesions are not accessible, serologic examination to detect antibodies or antigens may be a complementary diagnostic tool. Traumatic ulcers, necrotizing ulcerative gingivitis or stomatitis, syphilis, tuberculosis, squamous cell carcinoma and other mycoses, such as paracoccidioidomycosis should be considered as differential diagnosis. The reported case was confirmed by histopathology with PAS staining. HIV1 and HIV2 were also excluded.

Though spontaneous remission of oral histoplasmosis is reported, failure to treat the infection in patients with AIDS may result in death. Hidden immunosuppression should be considered always especially in HIV infection. General practitioners must exercise caution when examining patients, because oral lesions of histoplasmosis may be the only sign of AIDS. The basic inflammatory response in a deep fungal infection is granulomatous, with macrophages and multinucleated giant cells dominating the histologic picture. Diffuse, small granulomas contain a variable number of yeastlike *H. capsulatum* cells, which are highlighted by methenamine silver and PAS staining¹.

Histoplasmosis as systemic disease is treated by intravenous amphotericin B, which should be administered in a hospital because of its varied adverse effects, such as nausea, chills, fever, vomiting and renal complications. On the other hand, new and less toxic

antifungal agents are available, such as the oral azoles, which are the drugs of choice for long-term maintenance therapy. Negroni and colleagues reported that treatment with itraconazole was favorable for localized oral lesions, when no systemic signs or symptoms could be detected. This drug appears to be safe and effective for both induction and maintenance therapies, with less toxicity than that of amphotericin B. Similarly our reported case was treated by oral itraconazole with maintenance therapy. The disease responded well with regaining normal oral mucosa form and function and also improvement of general health.

Conclusion

Histoplasmosis usually affect immunodeficient individual, knowledge of the oral manifestations of histoplasmosis might enable clinicians to make earlier diagnoses and initiate therapy more quickly. It is important for general dental and medical practitioners to perform thorough clinical examinations and include histoplasmosis in the differential diagnosis of any persistent ulcerated oral lesions of both immunodeficient and immunocompetent patients.

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