

OBESITY AND RENAL DYSFUNCTION

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Abstract: Obesity is now major public health problems even in developing nations like India, with prevalence ranging from 10-50% been reported in various studies. Obese patients are well known to be at high risk of hypertension and diabetes, both are an independent risk factors for Chronic Kidney disease (CKD) Studies in recent years have highlighted that obesity has direct effect on renal functions. Morbid obesity causing FSGS leading to nephrotic syndrome has been described. Recently, obesity related Glomerulopathy have been described which presents with proteinuria mainly non-nephrotic range, it has a more benign course and slowly progresses to renal failure. It is a morphological distinct entity with subtle glomerular change unlike FSGS. It is still unclear whether increase in BMI has direct relationship with CKD or it causes development of renal failure due to increase prevalence of hypertension and diabetes in obese patients. Studies have shown that increasing BMI increases the risk of CKD especially in younger males. Also studies have highlighted that increasing components of metabolic syndromes makes a person more likely to develop CKD. Although several studies have shown glomerular changes in obese patients but its exact pathogenic link is still under investigation, various mechanisms have been highlighted foremost being hemodynamic factors. Obesity has been proposed to cause increased Glomerular filtration rate (GFR) by causing hypoalbuminemia, by effect of RAS on glomerular capillaries and arterioles, though some studies have shown that obese patients with predominantly central obesity have less GFR as opposed to obese patients with more uniform fat distribution. Various mechanisms have been described for this although more data support hyperfiltration. Cardiopulmonary dysfunction in obese patients leading to decreased renal blood flow and causing RAS activation have also been suggested to have a pathogenic role in causing renal dysfunction. Recently role of various hormones and cytokines have been described in obese and metabolic syndrome patients leading to renal dysfunction. Leptins has been shown to be responsible for causing endothelial cell proliferation and elaborating mesangial matrix. Role of other inflammatory mediator such as IL-6, TNF-alpha, adiponectin have been described in causing glomerular injury. Insulin resistance has also been shown to have a role in causing efferent arteriolar constriction and promoting glomerular hypertrophy. Direct effects of lipids in causing renal epithelial and mesangial cell injury have also been described. Paradoxically, obese patients have shown better outcome during dialysis and renal transplantations due to better nutritional status but morbid obesity makes the prognosis poor. So weight loss is the cornerstone of preventing renal dysfunction in obesity Though various medications in the form of thiazolidinediones and RAS inhibitors have been used, but treatment needs to be individualized. HMG COA reductase inhibitors have been shown to have reno-protective effect on some studies.

INTRODUCTION

Obesity is now being recognised as a public health problem worldwide. More than two-thirds of American adults are overweight or obese¹. Changes in diet coupled with an increasingly sedentary lifestyle have sparked off an epidemic of obesity in several Asian countries including India². There is a paucity of nation wide data regarding the magnitude of this problem in India, however several published studies have reported a prevalence ranging from 10-50%³. Obesity is a link between insulin resistance and the other components of metabolic syndrome i.e. diabetes, hypertension and dyslipidemia. It is a well-recognized risk factor for diabetes and hypertension, the two most common etiologies of chronic kidney disease (CKD). Obesity was shown to strongly correlate with the prevalence of hypertension in both males and females in the Framingham study⁴. The landmark INTERSALT study also showed an association between body mass index (BMI) and blood pressure⁵. Prevalence rates of type 2 diabetes increase steeply across BMI categories, especially among women⁶.

Over the years, both experimental and clinical studies have brought forth evidence to suggest that obesity has a direct deleterious effect on renal function, increasing the risk of renal injury and CKD. Recognizing obesity as a risk factor for CKD

is important, as it would suggest a definite intervention to reduce the risk of development and progression of CKD.

OBESITY RELATED GLOMERULOPATHY (ORG)

The renal effects of obesity in experimental animals and humans include both structural and functional adaptations, such as increased GFR, increased renal blood flow, and renal hypertrophy^{7,8}. In 1974, an association between massive obesity and nephrotic-range proteinuria was first reported⁹. Since that time, the development of glomerulomegaly and focal segmental glomerulosclerosis (FSGS) has been linked to 'massive obesity'. Experimental studies on the obese Zucker rat has shown the development of nephrotic range proteinuria, glomerulosclerosis, and progressive renal failure¹⁰.

A review of 6818 native kidney biopsies¹¹ identified 103 cases of ORG and showed that it is distinct from idiopathic FSGS. ORG when compared to idiopathic FSGS, presents with proteinuria, but has a lower incidence of nephrotic range proteinuria and nephrotic syndrome and a more benign course with slower progression to renal failure. Morphologically it shows consistent presence of glomerulomegaly, milder foot process fusion, lower percentage of glomeruli affected by segmental sclerosis and a predilection for perihilar sclerosis. It was also reported to manifest with glomerulomegaly alone. 45% ORG biopsies showed focal glomerular basement membrane thickening and focal mesangial sclerosis as seen in

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early diabetic nephropathy.

The first line of therapy in ORG should be weight reduction, which alone can reduce proteinuria. Lipid lowering agents, especially HMG-CoA reductase inhibitors, are effective in reducing mesangial sclerosis and proteinuria in obese Zucker rats¹⁰, however their role in humans remains to be defined. ACE-I has been shown to be effective in reducing proteinuria in obese populations¹¹. Longer follow-up will be required to determine the potential benefits of prolonged ACE inhibition in allaying progression to end-stage renal disease (ESRD) and preventing the possible evolution of ORG to FSGS.

OBESITY AND PROTEINURIA

Proteinuria has been identified as a significant predictor of end-stage renal disease (ESRD)²⁰. Microalbuminuria is a predictor of nephropathy in diabetic patients and is associated with renal functional abnormalities in non-diabetic subjects^{21,22}. Signs of early endothelial dysfunction manifested as microalbuminuria was independently associated with central obesity²³. In a study involving more than 5000 subjects in Okinawa²⁴, hypertension and diabetes mellitus were superior to obesity in predicting the development of proteinuria in all subjects but when stratified with men and women, obesity was a significant risk factor for the development of proteinuria independent of both hypertension and diabetes mellitus in men.

OBESITY AND CKD

It is still unclear whether increased BMI itself and renal failure actually have a cause-effect relationship or just the association as obesity leads to the two major causes of CKD, i.e. diabetes and hypertension.

EPIDEMIOLOGY OF OBESITY AND CKD

Over the years, several epidemiological studies have reported an association between obesity and CKD. The Framingham study initially reported an increased risk of new onset CKD with the increase in BMI in both males and females⁴. Looking at metabolic syndrome as a whole, Chen et al, in a population based study²⁵ of more than 6000 adults in the Third National Health And Nutrition Examination Survey (NHANES III) showed that the risk of CKD and microalbuminuria progressively increased with increase in the number of components of the metabolic syndrome and it was an independent risk factor for CKD. In a Swedish study²⁶, Ejerblad et al analysed the anthropometric data in a nationwide case-control study of incident moderate CKD. Overweight (BMI ≥ 25 kg/m²) at age 20 was associated with a significant three-fold excess risk for CKD, relative to BMI < 25. Obesity (BMI ≥ 30) among men and morbid obesity (BMI ≥ 35) among women anytime during lifetime was linked to three- to four-fold increases in risk. The strongest association was with diabetic nephropathy, but two- to three-fold risk elevations were observed for all major subtypes of CKD. A study²⁷ of a large cohort of 320252 adults who volunteered for health check up in Northern California also showed that a higher baseline BMI

was an independent predictor of ESRD even after adjusting for confounding factors including baseline blood pressure level and the presence or absence of diabetes mellitus. Thus, although hypertension and type-2 diabetes are important mediators, additional pathways also may exist. Iseki et al²⁸ examined the relationship between obesity (i.e., BMI) and CKD or ESRD using a community based screening registry in Okinawa, Japan and found that incidence of ESRD increased when BMI increased, particularly in men. In the hospital-based screening study²⁸, the number of components of metabolic syndrome was significantly related with the prevalence of CKD. Thus the Asian experience also supports the obesity-CKD hypothesis.

PATHOPHYSIOLOGY OF RENAL FAILURE IN OBESITY

Several studies have reported an association between obesity and CKD and experimental and clinical studies have delved on the glomerular changes in obese subjects. But the exact mechanistic link is complex, though we have gained some valuable insights from recent studies.

1. Hemodynamic Factors

Haemodynamic factors play a significant role in obesity-induced renal dysfunction. This includes hypertension and other plausible phenomena, which need to be explored

• Obesity, Hypertension and Renal Dysfunction:

Epidemiological studies have demonstrated a direct relationship between obesity and hypertension^{4,5}. Although the complex mechanisms causing obesity related hypertension have not been completely elucidated, hypertension and renal injury are mutually related in obesity. Several studies have shown a hypertensive shift in pressure natriuresis in obese subjects^{7,29,30}. This is mainly due to increased tubular reabsorption of sodium, secondary to increased glomerular filtration rate (GFR) and renal plasma flow^{30,31}. Increased sodium reabsorption associated with weight gain has also been attributed to: (1) increased renal sympathetic activity, (2) activation of the renin-angiotensin system, and (3) altered intrarenal physical forces (increased intra-renal pressure due to fat surrounding the kidney and obesity induced histologic changes within renal medulla)³¹. Although hyperinsulinemia was postulated to cause elevated arterial pressure in obese subjects, subsequent evidence have failed to link chronic hyperinsulinemia and hypertension³³. Recent studies have also highlighted the importance of leptin and angiotensinogen in pathogenesis of obesity associated hypertension³⁷. Ribstein et al also showed that obesity magnifies the effect of hypertension on albuminuria, with a steeper regression line between albumin excretion rate and arterial pressure in overweight compared to lean hypertensive subjects, suggesting that obese hypertensive patients are susceptible to the development of renal damage which further perpetuates and worsens the hypertension¹⁴.

- **Hyperfiltration:** Studies in animals and in humans have shown that obesity is associated with elevated GFR and increased renal blood flow^{7,13,30} leading to increased filtration fraction. Elevation in GFR may be mediated in part by increased protein consumption. Afferent arteriolar dilation coupled with efferent renal arteriolar vasoconstriction as a result of elevated Angiotensin II causes increased transcapillary hydraulic pressure gradient. This leads to hyperfiltration, glomerulomegaly, and later focal glomerulosclerosis¹¹. Obesity precipitates renal failure in those with reduced renal mass by hyperfiltration injury. In 54 patients with unilateral renal agenesis or remnant kidney, obesity was the only clinical variable statistically associated with the development of proteinuria and progression of renal failure¹². Bagby et al¹⁶ suggested that intrauterine growth restriction may lead to decreased nephron number and impaired kidney development, which if coupled with an excessive infant “catch-up” growth after birth may result in a mismatch between body size and nephron number. This would predispose to nephron hyperfiltration and hypertension later in life. A significant role of obesity in the progression of IgA nephropathy has been reported¹⁸. However, sub analysis of the MDRD study did not find any significant influence of baseline BMI on the progression of chronic renal insufficiency¹⁹.
- **Hypofiltration:** Paradoxically not all studies have shown an increase in GFR and renal blood flow in obese individuals. The pattern of obesity has been found to affect renal hemodynamics. An elevated BMI with central obesity results in reduced GFR, increased renal vascular resistance, and reduced effective renal blood flow as opposed to obesity with peripheral fat distribution^{37,38}. So hyperfiltration may not be the norm in obese subjects, and values need to be interpreted in light of body fat distribution and method of GFR adjustment. Raised intra-abdominal pressure also causes increased intrathoracic pressure, impaired right ventricular filling, pulmonary hypertension, and diminished cardiac output, all of which may impair renal perfusion. Also, increased fat in the renal hilum may compress renal vessels and renal parenchyma, causing elevated renal interstitial fluid hydrostatic fluid and slower renal blood flow and renal tubular flow rates, as shown in obese dogs³⁰. Though more data support hyperfiltration as the main contributor to renal dysfunction in obesity, hypofiltration is plausible, and more studies are needed to dwell on this hypothesis.

2. Cardiopulmonary factors:

Morbidly obese patients commonly have pulmonary hypertension, obstructive sleep apnoea, and cor-pulmonale³⁹, which increase right ventricular overload and again cause increased venous pressures, including increased inferior vena caval and renal vein pressures. In addition, cardiac dysfunction, particularly impaired right ventricular function⁴¹ and, to a lesser

extent, left ventricular function, has been described in patients with obesity. This has been attributed to impaired cardiac hemodynamics and direct myocardial lipotoxicity. Impaired cardiac output decreases renal perfusion. Together, these hemodynamic effects may contribute to activation of the RAS, renal sodium retention, and possibly hypertension and renal dysfunction

3. Obesity-metabolic syndrome-inflammation

Visceral adipose tissue is an endocrine organ and a site for elaboration and secretion of hormones and cytokines⁴³. It is associated with a chronic, low-grade inflammatory state, suggesting that inflammation may be a potential mechanism whereby obesity leads to insulin resistance^{37,43}. Since insulin is an anti-inflammatory hormone, insulin resistance per se promotes inflammation leading to a vicious cycle. In the NHANES III cohort⁴⁴, the presence of metabolic syndrome was associated with greater odds for inflammation for various levels of creatinine clearance. In a gene expression study of 6 patients with obesity, proteinuria and biopsy proven ORG, Wu. et.al.⁴⁵ found increased expression of genes that are related to lipid metabolism, inflammatory cytokines, and insulin resistance in their glomeruli compared to the glomeruli of age and gender matched control donor kidneys. These findings strongly suggest that inflammatory cytokines and lipid by-products affect renal function in obese patients, but this is yet to be proven definitively. Here we briefly review the cytokines playing a role in obesity induced renal injury:

Leptin: It is derived from adipocytes and is structurally similar to IL-2. Increased adiposity results in increased leptin levels^{35,36,43}. Leptin crosses the blood-brain barrier, where it decreases neuropeptide Y in the hypothalamus to suppress appetite and increase energy expenditure. In addition, it increases insulin sensitivity in various tissues. Patients with obesity and the metabolic syndrome are resistant to the hypothalamic effects of leptin and have elevated leptin levels. Leptin has direct as well as indirect effects on the kidney:

Direct effect: Because the short form of leptin receptor (Ob-Ra) is abundantly expressed in the kidney³⁶, leptin is being postulated to be responsible for renal injury in obesity. Recombinant leptin stimulates the proliferation of cultured glomerular endothelial cells (but not mesangial cells) and increases TGF- β 1 mRNA expression and production^{35,47} and when infused in rats produces significantly increased type IV collagen protein, glomerulosclerosis, and proteinuria without increasing BP. *So leptin may play a role in the glomerulosclerosis that is observed in obese patients with proteinuria and/or CKD, independent of hypertension.*

Indirect effects: Leptin increases sympathetic nerve trafficking and renal sodium retention, which may cause hypertension³⁶. Furthermore, it stimulates oxidative stress in endothelial cells and induces a proinflammatory state as a result of stimulation of Th1 cells^{36,49}. Such effects may promote atherosclerosis.

- **IL-6 and CRP:** Plasma IL-6 levels positively correlate with obesity and insulin resistance and predict the development

of type 2 diabetes⁴³. It mediates insulin resistance, increases platelet activity and atherogenicity, increases the expression of adhesion molecules on endothelial and vascular smooth muscle cells⁴³, and activates the local renin-angiotensin system (RAS)⁴⁸, thus promoting cellular injury. IL-6 also increases TGF- β 1 signalling *via* modulation of TGF- β 1 receptor trafficking, an effect that may enhance renal fibrosis⁴⁹. It also increases CRP production and new data suggest that CRP may not be just a marker of inflammation and cardiovascular risk but also a contributor to vascular damage and cardiovascular events³⁷.

TNF- α : TNF- α is produced by macrophages within adipose tissue, and its levels are elevated in the metabolic syndrome⁴³. TNF- μ is one of the mediators of insulin resistance in adipose tissue: It has been shown to mediate inflammation^{51,53} in several models of renal injury, including glomerulonephritis⁵⁰, acute renal failure⁵¹, and tubulointerstitial injury⁵². These cytokines may be toxic to renal epithelial, mesangial, and endothelial cells. However, the specific role of TNF- α in metabolic syndrome-induced renal injury has not been studied.

Adiponectin: Adiponectin is an adipokine with insulin-sensitising, anti-inflammatory and anti-atherogenic properties^{54,55}. Its levels correlate negatively with fat mass, body weight, BP, insulin resistance, inflammatory markers of the metabolic syndrome, and high triglyceride (TG) and LDL cholesterol levels and positively with HDL cholesterol and weight loss⁵⁵. Hypoadiponectinemia is associated with vascular dysfunction and with cardiovascular events in patients without CKD⁵⁶. It may thus protect various organs from the harmful effects of chronic inflammation. But studies have reported contradictory findings about the role of adiponectin in CKD. Becker et al.⁵⁷ found that low adiponectin levels in patients with mild or moderate renal failure were correlated with cardiovascular events, whereas Menon et al.⁵⁸ found that in patients with stage 3 or 4 CKD, all-cause and cardiovascular mortality were paradoxically higher in those with high adiponectin levels. The exact significance of adiponectin in the pathogenesis of CKD is still unclear.

4. Insulin resistance

Obesity is characterised by an insulin resistance state which forms the basis of the metabolic syndrome. This has multifaceted direct and indirect effects on the kidney. As insulin reduces norepinephrine-induced efferent arteriolar constriction, insulin resistance may increase the transcapillary pressure gradient by increasing efferent arteriolar resistance. Hyperinsulinemia also stimulates the synthesis of growth factors such as insulin-like growth factor (IGF)-1 and IGF-2, which may promote glomerular hypertrophy^{33,34}. Also, as we discussed earlier, insulin being an anti-inflammatory hormone, its resistance further promotes the milieu of inflammation thus promoting renal injury.

5. RAS

Activation of the RAS and increased circulating levels of renin, angiotensinogen, angiotensin-converting enzyme, aldosterone, and, to some extent, angiotensin II (Ang-II) are common in obese individuals despite sodium retention and an apparently increased extra cellular fluid volume⁵⁹. Several mechanisms have been implicated including sympathetic stimulation, hemodynamic alterations^{30,31} as discussed earlier and synthesis of several proteins of the RAS by visceral fat⁶⁰. Giacchetti et al.⁶¹ recently found a significantly higher expression of angiotensinogen and Ang-II type 1 receptor mRNA in visceral adipose tissue than subcutaneous fat of both obese and lean individuals. Also 5% weight loss in obese individuals resulted in significant reductions of circulating levels and adipose tissue expression of RAS hormones⁵⁹. The larger adipose tissue mass in obese individuals may be partly responsible for the increased circulating levels of RAS hormones. Ang-II is widely known to affect adversely progression of renal disease in several models of renal injury and in patients with CKD by causing hypertension, raised intraglomerular pressure, exacerbation of proteinuria, induction of intrarenal inflammatory cytokines and growth factors, and apoptosis⁶². It also increases insulin resistance and suppresses adiponectin levels in obesity⁶⁰. So Ang-II has a dual effect of promoting the various components of metabolic syndrome and directly injuring the kidney. But most of these observations are from animal studies and need validation in humans.

6. Renal Lipotoxicity

Studies suggest that lipids may cause renal mesangial and epithelial cell injury and may promote renal disease progression^{63,64}. HMG-CoA reductase inhibitors have been found to improve proteinuria and preserve renal function⁶⁵, suggesting a role for lipids per se in promoting renal injury. The mechanisms of renal lipotoxicity are not fully elucidated, but a number of experiments suggested a role for TG-rich lipoproteins, FFA and their metabolites, and albumin-loaded FFA in renal cell injury.

OBESITY AND DIALYSIS

In contrast to the general population, a high BMI is associated with better outcome in dialysis patients^{66,67}. This is known as a 'risk factor paradox' or 'reverse epidemiology' for cardiovascular disease in uremic patients⁶⁸. However some studies have shown that high BMI dialysis patients with inferred high body fat actually had increased prevalence of atherosclerosis and increased mortality⁶⁹. Thus there is conflicting data on effect of obesity on dialysis patients. It is hypothesized that nutrition exerts a much stronger influence on survival than atherosclerosis in CKD⁷⁰. Malnutrition strongly increases the risk of death, while better nutrition gives survival benefit. So risk of death is highest in malnourished patients (low muscle and low fat mass) and lowest in well-nourished patients (high BMI, high muscle mass). Though obesity (high BMI, high fat mass) increases the risk of

atherosclerosis-related death, but the risk is not as high as malnutrition related death. So CKD patients with high body fat have intermediate survival.

OBESITY AND RENAL TRANSPLANTATION

The impact of obesity on kidney transplant outcomes continues to be controversial. Some studies⁷¹ suggest that extremes of very high and very low BMI before renal transplantation are important risk factors for patient and graft survival and in this particular study elevated BMI was significantly associated with worse graft survival independent of patient survival. While in other studies there are no significant adverse effect of obesity on renal transplant outcomes except an increase in wound complications, which were generally of minor consequence. Obesity seems to influence delayed graft failure, graft survival, and patient survival. A body mass index of 35 kg/m² or more is significant for greater post transplant complications, especially new-onset transplant diabetes mellitus, wound complications, and post transplant weight gain. It is suggested that any association of obesity with reduced patient survival in renal transplant recipients is mediated in part by its clustering with traditional cardiovascular risk factors such as hypertension, dyslipidemia, insulin resistance and post transplant diabetes mellitus, but what is not understood is what mediates the association of obesity with graft failure. Whether it is the higher incidence of cardiovascular co morbidities jeopardising the graft or factors specific to obesity, such as hyperfiltration and glomerulopathy, that might be implicated, currently remains unknown. It can be concluded, however, that pre- and post transplant obesity should be targeted as aggressively as the more well-established cardiovascular risk factors in order to optimise long-term renal transplant outcomes.

POTENTIAL INTERVENTIONS TO PREVENT OBESITY INDUCED RENAL DYSFUNCTION

Weight loss and increased activity are the cornerstones of the treatment of obesity and the metabolic syndrome. Many other targeted interventions may be adopted. Bariatric surgery and surgical resection of abdominal adipose tissue improve the metabolic profile and reduce inflammatory cytokine levels both in the short term and up to 10 yr later³⁷. However, the long-term safety of these procedures has not been established. PPAR- μ (the fibrates) and PPAR-I (the thiazolidinediones) agonists improve insulin sensitivity, but they are not without risks in the setting of renal disease and are known to cause myopathy and salt and fluid retention myopathy and sodium and fluid retention respectively. Blockade of the RAS is likely to be beneficial, but treatment will need to be individualized depending on the degree of renal dysfunction and the presence of other co morbidities. HMG-CoA reductase inhibitors have been renoprotective in some studies⁶⁵. Large, randomised, controlled trials to examine the effects of each of these

interventions on renal function in patients with the metabolic syndrome are needed before any firm recommendations can be made.

CONCLUSION

Obesity and metabolic syndrome are independent risk factors for CKD. Large-scale experimental and clinical trials are needed to understand the various mechanisms causing obesity induced renal dysfunction to propose definite targeted interventions for its prevention and treatment. As of now all obese patients should be advised weight reduction along with blood pressure and blood glucose control to prevent and treat all forms of kidney disease

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LITERATURE REVIEW

ATTITUDE OF HEALTH CARE PROFESSIONALS TO BRAIN DEATH: INFLUENCE ON THE ORGAN DONATION PROCESS. Jonathan Cohen, Sharon Ben Ami, Tamar Ashkenazi and Pierre Singer *Clin Transplant* 2008; 22: 211–215.

The acceptance and application of the concept that brain death is a valid determination of death is the central issue in organ donation. However, whether attitude to brain death of health care professionals influences the organ procurement process has not been systematically studied. Questionnaires were distributed to health care professionals involved in the organ procurement process (intensive care, internal medicine, emergency room, anesthesia) in all hospitals in Israel. Attitude to brain death (defined as positive if the respondent accepted brain death as a valid determination of death, negative or do not know) and level of comfort in performing key donor-related tasks were analyzed. A total of 2366 completed questionnaires were returned (629 doctors and 1737 nurses; response rate 60.3%). Overall, 78.9% of respondents had a positive attitude to brain death. This was significantly associated with increasing age, higher professional status and was most prevalent amongst intensive care unit staff ($p < 0.001$ for all variables). These respondents felt significantly more comfortable informing the transplant coordinator of a potential donor, explaining brain death to the family, raising the subject of organ donation, approaching the family about donation and providing support to the grieving family. In addition, they believed the transplant coordinator should be involved early in the donation process. The understanding and acceptance of brain death as a valid determination of death was associated with a positive effect on the level of comfort of health care professionals in performing key donor-related tasks. Reinforcing a positive attitude to brain death among health care professionals may facilitate the procurement process.