CLINICAL VIGNETTE

The Medically Complex Living Kidney Donor

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Background

Three decades of advancements in kidney transplantation have improved morbidity, mortality, and quality of life for individuals with kidney failure[1]. Despite the advantages of transplantation, barriers still persist, including the major obstacle of limited organ supply. There are currently over 95,000 individuals on the kidney transplant waiting list, with 17,000 kidney transplants performed in 2010. This mismatch has caused increased transplant waiting times. Patients with end stage kidney disease, now have a median time to transplantation 40 months. (Figure 1) Longer waiting times result in increased mortality and poorer graft outcomes following transplantation.

Increasing donor supply is needed to improve outcomes in end-stage renal disease. However, achieving this goal remains challenging. Between 1980 and 2007 the prevalence of ESRD increased over three fold, from 100 per million to 335 per million. Unfortunately, the number of deceased donor organ transplants has remained stable. Faced with the ongoing organ shortage, and an ever increasing demand, living donation gained recognition as an alternative to fill the gap. This was further supported by superior outcomes in living kidney transplantation[2]. In 1988 the number of living donors was approximately 1800/year, which increased to over 6000/year by 2004. This initial increase was embraced by the transplant community as the solution to the organ deficit. However, by 2004 living kidney transplant rates began to level to its current rate of approximately 6600 per year. Despite the almost doubling of available organs, patients are still faced with inordinate waiting list times.

Continued demand has led to several innovative solutions, including: expanded criteria for deceased organs, desensitization protocols, and paired donor chains. Another potential solution to the shortage is expanding the living donor pool. The living donor pool has largely remained restricted to the "perfectly healthy" individual without medical illness or anatomical abnormalities. Initially safety of living kidney transplantation was extrapolated from observational studies of unilateral nephrectomy in young trauma patients. The limited risk of developing ESRD and HTN was assumed to carry over to the healthy living kidney donor. Recently, long term studies on the safety of living kidney donation have been conducted and suggest that living donation is relatively safe for well selected donors. Surgical complications have been reported with 90-day death rates between 0.02 to 0.04%[3-5] and long term mortality similar to the general population[6]. Initial observational studies indicate that in the well selected living kidney donors the risk for kidney failure and hypertension is also similar to the general population[7,8]. However, these studies are limited by incomplete donor follow up, lack of a proper control group, and varying severity of disease, making it difficult to determine the additional risk conferred on "healthy" donors. Relaxing the acceptance criteria for donation may improve the supply but at an unacceptable cost to donors.

Large-scale demographic changes in the United States have reduced the number of "perfectly healthy" donors from decades ago, from which most long term knowledge on donor safety is derived. Since the 1980s there has been a change in the "average" American, to a more ethnically diverse, older, and obese society. During this period changes to the standard definitions of certain diseases and improvements in diagnosis have led to an increase in the prevalence of hypertension, diabetes, and kidney stones. These changes have placed additional restrictions to donation, which may lead to inappropriate exclusion of living donors.

This paper will review the safety evidence for donors with isolated medical problems and those from high-risk ethnic backgrounds. It will discuss the safety of donation from the so called "medically complex living donors"[9,10], which include elderly donors (age > 60), donors with well controlled hypertension, glucose intolerance, obesity, prior history of renal calculi, and black and Hispanic donors. These patients have a higher baseline risk of short term surgical complications and/or long term risk of developing chronic kidney disease and hypertension.

However, the additional risk incurred by these donors is not known, and it remains to be seen if careful selection within this population can minimize this risk, and if any additional risk is reflected in clinical outcomes.

The Elderly Donor

Traditionally, potential donors over the age of 60 have been excluded from donation. The impetus for exclusion is based on observational data suggesting unacceptably high risks of donation. This is compounded by concern that organs from the elderly are inferior to those from young healthy donors. Several observational studies confirm an increase in short-term surgical mortality in the elderly, compared to younger patients undergoing the same procedure[11]. The elderly also appear to carry a higher risk of long term complications. There is a gradual decrease in glomerular filtration rate of 1 ml/min/1.73m^2/year after the age of 40, which results in a large portion of the elderly having chronic kidney disease. Kidney donation causes an immediate decrease in GFR by 20 to 30%[1], which would further potentiate this renal decline. In addition to the elevated risks to the donor there are concerns over the quality of donated elderly organs. There is an age-associated decline in kidney function which may result in reduced allograft longevity. Proof in concept is the reduction in allograft survival associated with expanded criteria kidney organs, which include in their definition an age > 60 years. While these concerns are valid, new data suggest they may be exaggerated, in part due to the overestimation of the aging effects in otherwise healthy older patients and minimization of risk by careful selection.

The elderly comprise the largest growing population in the United States since 1970 (Figure 2), and make a logical target to increase the donor pool. While the prevalence of chronic kidney disease is greater in this group, its consideration as a true disease is likely overestimated. In the past 20 years there has been a growing awareness of kidney disease. Population data extrapolated from the National Health and Examination Survey indicate an increasing prevalence of chronic kidney disease, from a prevalence of 10% between 1988-1994 [NHANES III] to 13.1% from 1999-2004 [NHANES IV]. Patients over the age of 60 constitute 40% of all patients with chronic kidney disease[13].

Some of this increase has been attributed to the higher prevalence of diabetes and hypertension, but changes in the definition of chronic kidney disease also contributed. A large part of this increase is the result of population wide implementation of creatinine based estimation equations. While the use of these equations have been an important means for screening and identifying patients with renal disease, they have led to a disproportionate increase in the elderly. One of the main criticisms of the current MDRD method of estimating GFR from serum creatinine is that it underestimates function in the elderly[14]. In 2002 the KDOQI staging guidelines for CKD were released, and became a billable item in 2005. NHANES data show that the definition change correlated with a large increase in diagnosis of CKD with a predominant rise in the mild category, eGFR 60-89 ml/min between NHANES III and IV (Figure 3). While these patients have reduced function the majority do not proceed to end stage renal disease. Fortunately, ESRD rates are < 1% in the elderly and the rates were higher for those individuals > 60 year of age compared to those > 70 years of age, 0.75% versus 0.33%, respectively[15]. The onset and progression of kidney disease may be exaggerated by this classification scheme. By selectively screening for only the healthiest elderly donors with normal renal function we can remove the effects of hypertension and diabetes, which are also highly prevalent. Population studies indicate that these patients have a low rate of proceeding to ESRD, especially in the absence of proteinuria.

Emerging data suggest the additive risk incurred by well selected elderly donors is minimal[16,17]. Small short term studies found donor nephrectomy in the elderly does not increase mortality, although there is a small but significant increase in the postoperative length of stay. This directly contradicts observational studies of the elderly, which suggest that selection can minimize the increased mortality seen with elective surgery and age. The long-term risk and organ quality from elderly donors was recently evaluated by Kumar et al[18]. This retrospective analysis examined the outcomes of living donors over the age of 55 and compared them to living donors < 45 years of age. Outcomes included allograft function and donor outcomes. The analysis revealed no significant difference in the outcomes of elderly donors compared to younger donors in terms of death and renal function at both one year and five years post donation. Furthermore, allograft survival was 92.8% vs. 88.5% at one year and 72.7% and 75.1% at five years for elder and younger donor organs, respectively. The only notable difference was a reduction in allograft GFR from elderly donors, which occurred post transplantation but remained

stable throughout one year follow up[19]. These data suggest that by carefully evaluating donors over the age of 60 the risk of donation can be minimized while also providing a suitable organ for transplantation.

The Hypertensive Donors

Chronic hypertension is a leading cause of cardiovascular disease, stroke, and chronic kidney disease[20]. Hypertension is currently defined as a blood pressure > 140/90 mmHg on three separate occasions, or the use of anti-hypertensive drug therapy. The risk for ESRD has been shown to begin with a systolic blood pressure > 140 mmHg with a 16% incremental risk for every 10 mmHg increase in systolic blood pressure[21]. Patients with blood pressures below this level also have an increased risk, but only those who develop hypertension. Potential donors with hypertension have been excluded from donation given the strong association between hypertension and incident ESRD.

The prevalence of hypertension has increased by 18% over the past two decades, from 24.4% to 28.9% of the population[22]. It is estimated that 40% of the US population will be diagnosed with hypertension by the year 2050. This increase has the potential to severely impact the living kidney donor pool. However, changing definitions of hypertension and the improvements in treatment have led several groups to reconsider the strict exclusion of all hypertensive patients.

The definition of hypertension has changed significantly over the past 30 years (Figure 4). Hypertension was initially defined in 1977 as a diastolic blood pressure > 105 mmHg with no mention of systolic blood pressure until 1984, when hypertension was revised as a blood pressure > 160/90 mmHg. The current definition of hypertension did not exist until 1993[23]. The stricter definition of hypertension has contributed to the increase in prevalence. Along with the increase in prevalence there has been a marked improvement in the treatment of hypertension. Compared to 1988, current NHANES data show the treatment of hypertension has increased from 61% to 73% and control, defined as a systolic blood pressure < 140 mmHg and a diastolic blood pressure < 90mmHg, improved from 35% to 50%[22]. Treatment also has been more successful with an average decrease in mean systolic and diastolic BP of 7 and 4 mmHg in the same period. Improvements in management of hypertension reduce the risk of ESRD and would potentially allow for the inclusion of well-controlled hypertensive patients.

The inclusion of well-controlled hypertensive patients is estimated to increase the donor pool by 14%. Long-term data also suggest that living kidney donation imparts no additional risk of hypertension when donors are compared to the general population[24]. Much of this data represent patients from before 1993 and it is likely that several of those donors would be considered hypertensive and excluded from kidney donation using today's criteria. There are several concerns extrapolating these results to all donors. As data from individual donors were not available it is unclear if donors who are now considered hypertensive disproportionately developed hypertension. Furthermore, hypertension that developed in donors during that period was approximately 5 to 10 mmHg higher than in the general population, which would impart a 16% increase in ESRD. However, this additional risk may actually be attenuated in the era of improved blood pressure management.

Despite these considerations, short-term data on hypertensive kidney donors indicate that donor risks can be minimized. In a retrospective analysis of hypertensive kidney donors at the Mayo Clinic, moderately hypertensive donors with normal kidney function did not have differences in blood pressure, GFR, or urinary protein excretion during the first year of kidney donation[25]. While these patients appear to have similar outcomes to matched cohorts after one year, the development of hypertension and CKD often take decades before they become apparent. Long term follow-up in an era with more stringent definitions of blood pressure and improved control will be needed to help determine the presence of any additional risk assumed by the hypertensive donor.

Pre-diabetes

Diabetes is the most common cause of chronic kidney injury and end-stage renal disease. The number of diabetics has increased in the past several decades from approximately 5.6 million in 1980 to 25.8 million in 2009, corresponding to rise in prevalence from 5% to 8.3% of the US population. The lifetime risk of chronic kidney disease in diabetics is estimated at 25% to 50%[26]. Given this substantial increased risk, potential donors undergo extensive screening for diabetes, and diabetes in a potential living donor is clear contra-indication to donation.

Improvements in diagnostics and a heightened awareness for identifying at risk patients resulted in the emergence of a new disease entity, "pre-diabetes". These patients do not meet the standards for the diagnosis of diabetes, i.e. fasting glucose > 126 mg/dL or 2 hour glucose following a oral glucose tolerance test of > 200 mg/dL, but do have elevated serum glucose levels. Initially known as borderline diabetes, this term was replaced by the terms impaired glucose tolerance and impaired fasting glucose in 1997. In 2002 these terms were replaced by "pre-diabetes" in order to emphasize increased risk associated with progression to diabetes. The current definition of pre-diabetes is the presence of either a fasting glucose between 100 mg/dL to 125 mg/dL, formerly known as impaired fasting glucose, or a two hour glucose level of 140 mg/dL to 199 mg/dL following a 75 gram oral glucose load, formerly known as impaired glucose tolerance.

The presence of pre-diabetes is not without risk. Patients with pre-diabetes may progress to overt diabetes, with a 50% risk within 10 years of diagnosis of pre-diabetes[27]. In comparison, patients with diabetes have a 33% prevalence of CKD and those without diabetes or pre-diabetes have a substantially lower prevalence of 12%[28]. The risks of diabetes and CKD have led to recommendations that potential donors found to have pre-diabetes be excluded.

Roughly 57 million, or 18.9% of the United States population, have pre-diabetes[29], which increased from 6.9% in 1990. More recently a hemoglobin A1C value between 5.7 and 6.4% has been used to diagnose patients with pre-diabetes. The inclusion of hemoglobin A1C in the definition of "pre-diabetes" increases the estimated prevalence to 79 million individuals (Figure 5), bringing the combined prevalence of diabetes and pre-diabetes to > 35% of the United States population. This number is expected to increase further during the next decade to over 50%, which would further increase the number of individuals with CKD while limiting the donor pool.

Given the shortage of organs some centers have started accepting carefully screened individuals with pre-diabetes despite the increased risk of developing diabetes and chronic kidney disease, arguing that the selection process can minimize these risks. A retrospective analysis of Japanese living donors with glucose intolerance by Okamoto and colleagues supports this concept[30]. They divided 444 living donors into three groups based on a 75 gram oral glucose tolerance test, 373 patients had no evidence of pre-diabetes or diabetes, 44 had pre-diabetes and 27 had diabetes. The groups were compared for perioperative complications, mortality differences, and the development of chronic kidney disease and ESRD. Perioperative complications and survival rates at years 5, 10 and 20 were compared and found to be similar between all groups. Furthermore, all 44 pre-diabetic and 27 diabetic donors had yet to develop complications of diabetes, including CKD and ESRD, by the end of the follow up period, a mean of 88 months. The majority of these patients had close physician follow up, underscoring the need to provide continued care for these individuals in order to minimize their risk.

The Obese and Overweight Donor

The weight of a potential living donor provides several challenges and risks. Increases in body-mass-index (BMI) have been associated with worse postoperative outcomes, including mortality, length of stay, and postoperative infection risk. In addition to the increase in short term surgical risk a BMI greater than 25 kg/m2, the threshold for a diagnosis of overweight, is associated with an increase in hypertension, diabetes, and dyslipidemia. Clustering of these conditions is known as metabolic syndrome, and has been linked to increased cardiovascular and chronic kidney disease risk[31]. Metabolic syndrome is seen in 30% of individuals with a BMI 25-29.9, classified as overweight, which increases to over 65% in obese patients, defined as a BMI > 30 kg/m^2, [32].

Obesity itself is associated with chronic kidney disease in the absence of hypertension and diabetes. In a landmark study Ejerblad et al[33], a history of BMI > 25 kg/m2 at the age of 20 was associated with a three-fold excess risk for developing CKD compared to patients with a BMI < 25 kg/m2. A BMI > 35 kg/m2 at any time was associated with a four-fold increase in this risk. Diabetes was responsible for a large portion of this risk, but multivariable analysis revealed that obesity alone led to a two-fold increased risk of developing CKD. Given these risks, living donor BMI between 30 and 35 kg/m2 has been accepted as a relative contra-indication to donation.

Unfortunately, obesity is a growing epidemic in the United States. The prevalence of obesity has been increasing since 1960, when it was estimated that 12.8% of the population was obese. It is now

estimated that 25% to 30% of all Americans are obese. The most marked increase occurred after 1988, when the definition of obesity changed from two standard deviations above the average BMI to a BMI of > 30 kg/m2 (Figure 6). The prevalence of overweight individuals appears to be steady between 30% and 35%. However, overweight individuals are also at increased risk for developing metabolic syndrome and CKD.

Obesity in the presence of metabolic syndrome appears to increase risk of chronic kidney disease, supporting exclusion of this group of individuals from kidney donation. However, the growing obesity epidemic, especially in the Southern United States, has led to a severe shortage in donor organs. Many centers will accept patients with a BMI > 30 kg/m2 without metabolic syndrome, because not all patients with a BMI > 30 kg/m2 develop metabolic syndrome, and risk of long term complications can be reduced.

In the largest study, Heimbach *et al* reviewed data on 553 donors and compared outcomes in obese and non-obese kidney donors in the laparoscopic era. Patients with a BMI > 35 kg/m^2 were defined as having a "high BMI"[34]. Short-term analysis found increased postoperative infections as well as operative time in obese donors[35]. However, the increase in operative time was only 19 minutes and no effect on mortality or conversion to open laparotomy was seen. One year follow up found no difference in renal function and rates of microalbuminuria 6-12 months post donation, supporting that screening and selection can minimize risk. Other observational studies suggest that recipients receiving kidneys from donors with a BMI > 35 kg/m^2 have an increased risk of delayed graft function[36]. Thus despite minimal surgical and short term risk to the donor, donation from patients with a BMI > 35 kg/m2 results in a significant negative impact to the recipient and the current recommendations for exclusion of donors with a BMI > 35 kg/m^2 appear reasonable. Utilization of healthy patients with a BMI between 30 and 35 kg/m^2 would provide an increase in the number of organs with what appears to be minimal short and intermediate term risk to the donor.

Kidney Stones

Patients with a prior history of kidney stones are often excluded from kidney donation because of high rates of disease recurrence and an increase the risk of developing chronic kidney disease[37]. In the general population the likelihood of another kidney stone is approximately 15% at one year, 35% at five years, and 50% at ten years. The risk following nephrectomy has been observed to be slightly lower, at 14% by 8 years post surgery in patients who underwent nephrectomy for kidney stone complications[38]. There are concerns that development of a kidney stone in a unilateral kidney increases risk for obstruction and kidney injury.

As with other chronic disease, the epidemiological data indicate that the lifetime prevalence of kidney stones has increased from 3.2% in 1980 to 5.2% in 1994[39] (Figure 7). Exclusion of this group would further deplete our already narrowing potential donor pool. The major concern underlying these data is detection bias. Advancements in imaging have increased detection of incidental kidney stones. Many of these stones have minimal clinical significance. Glowacki et al. estimated that 29.8% to 45.7% of all diagnosed kidney stones were found in asymptomatic individuals using ultrasound technique[40]. This number may be higher with non-contrast CT scans. Patients with asymptomatic stones and no prior history of previous stones have a much lower rate of subsequent kidney stone formation.

The increased detection of asymptomatic individual is of particular interest to transplant. These patients clearly do not have the same risk for recurrent disease and donation may be safe. Retrospective data from a single center indicate that accepting candidates who have not had a recurrence for 10 years or greater before transplantation or who have asymptomatic calculi but no metabolic abnormalities have negligible risk for disease recurrence. Donors were excluded if they had evidence of stones in the collecting system, bilateral stones, or stones > 10 mm in size. Careful screening of donors with a history of kidney stones appears to mitigate the risk of nephrolithiasis in a single kidney. While further study is needed, careful selection of donors with a remote history or small incidental kidney stones found on imaging would increase the kidney organ pool without incurring additional donor risk.

Race

Not all healthy living donors carry the same long term risk for chronic kidney disease. Epidemiological studies indicate that Black and Hispanic individuals have a four- and two times respective risk of developing chronic kidney disease compared to Caucasians[41]. Much of this increased risk can be attributed to higher rates of obesity,

hypertension, and diabetes in these minority groups but other genetic factors may also lead to an increased risk. The higher prevalence of kidney disease is further compounded by worse control rates, resulting in a disproportionate representation of these groups with ESRD. The disproportional representation of minority groups with ESRD places an added consideration for living donation, as related donors would potentially share these increased risks.

The population of the United States is becoming more ethnically diverse. Census data indicate that blacks and Hispanics make up 14.6% and 16.8% of the United States population. This is an increase from 11.7 % and 6.5% for each group since 1980. The projected increase in these populations, combined with the increased prevalence of chronic disease, will likely to continue to pressure our limited organ supply.

Lentine et al[7] retrospectively analyzed 4650 living kidney donors from October 1987 to 2007 using billing claims and compared them to their corresponding subgroups using NHANES data from 2005-6. Among the donors 13.1% were black and 8.2% were Hispanic. Living donors from these two groups experienced a significant post donation increase in the rates of hypertension, diabetes mellitus, and chronic kidney disease (adjusted hazard ratios of 1.52 CI 1.23 to 1.88, 2.31 CI 1.33 to 3.98, and 2.32 CI 1.48 to 3.62, respectively), compared to the reference Caucasian cohort. However, these risks were not elevated compared to a general healthy cohort adjusted for race. Thus it appears that careful donor selection does not impart any additional risk beyond those associated with racial variation and that donation by healthy high-risk ethnic groups is safe.

Conclusions

Rates of living kidney transplantation have increased in the past two decades as the benefits of living donation compared to deceased organ transplants have become apparent. Unfortunately, the prevalence of chronic kidney disease has also increased leading to the continued imbalance between supply and demand. The mounting pressure for organs has been further complicated by changes in US demographics and in medical science, which have combined to change what was once considered a "healthy" individual.
The US population is getting older, obese, and more racially diversified, changing what was considered as the "normal healthy" American. More stringent definitions for hypertension, diabetes, and kidney stones have led to an increased prevalence of these conditions, many of which would have been considered "healthy" in a prior era. Fortunately, treatments for these diseases have improved, and more individuals are being treated, and treated to goal. These changes may reduce the risks of complications associated with these conditions. As the strain on the organ supply continues the transplant community has looked towards relaxing previous stringent exclusion criteria to expand the donor pool. Initial studies demonstrate that careful donor selection and screening can minimize the associated long term risks of the medically complex donor and high risk racial groups to a rate similar to those of the "healthy" living donors.

Figure 1: Increase in median waiting list time for patients with AB Blood Type from 1988 to 2011. UNOS data from the years 1988 to 2011. The increase in median waiting time after listing increased from 412 days to 1409.

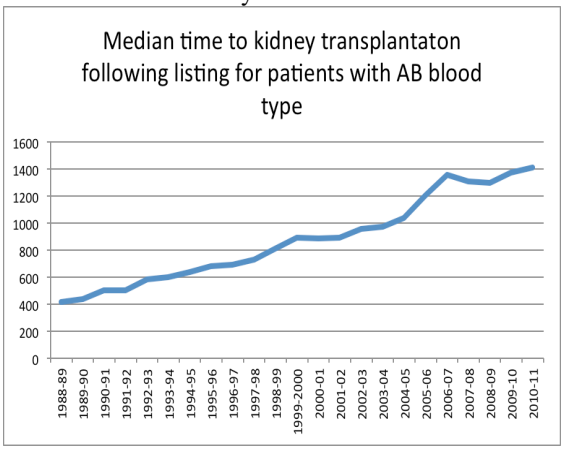


Figure 2: Change in Relative US Population distribution from 1970-2005.

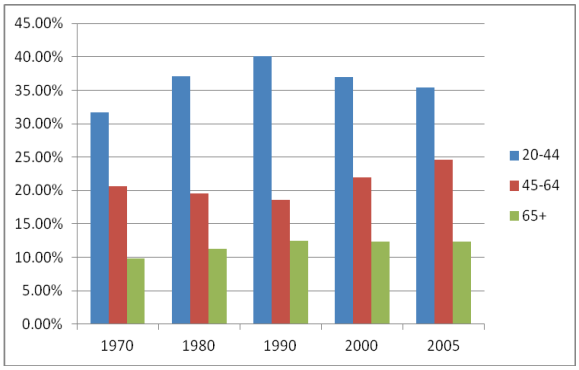
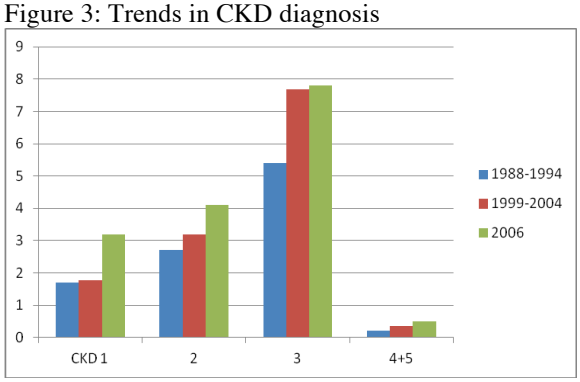


Figure 3: Trends in CKD diagnosis



1988-1994: MDRD
1999-2004: KDOQI guidelines 2002
2005: billing ICD-9 codes

Figure 4: hypertension prevalence

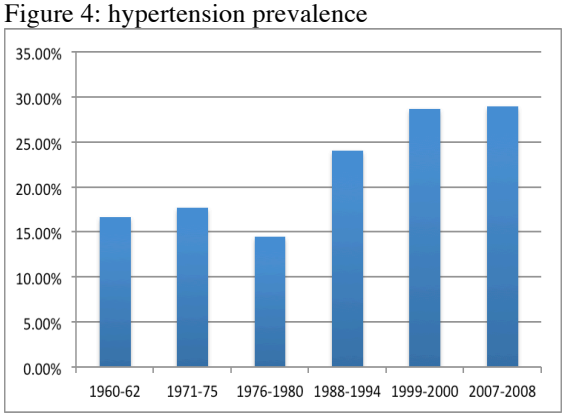


Figure 5: Diabetes Prevalence

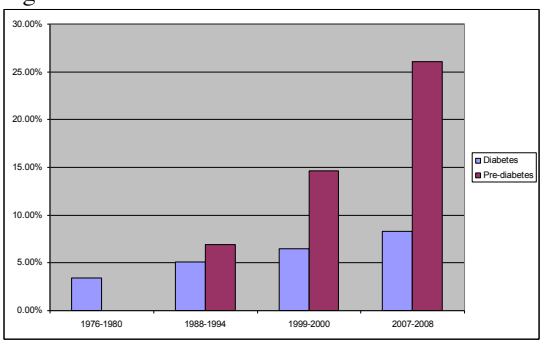


Figure 6: Obesity and Overweight Prevalence

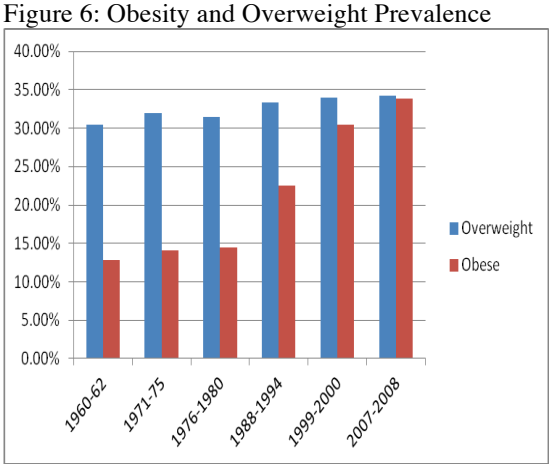
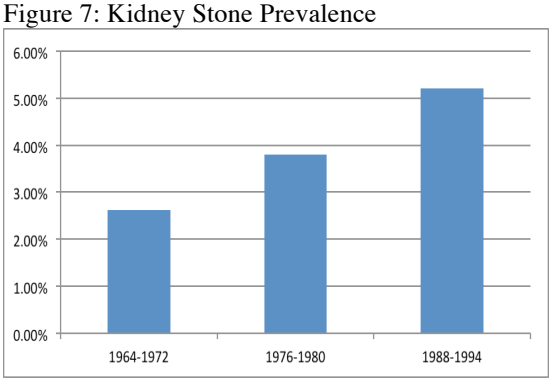


Figure 7: Kidney Stone Prevalence



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