Lithotripsy: benefits and unwanted side effects

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Dedication

To my wife Brenda, and my daughters Kaitlyn and Ashleigh; thank you for all your patience and understanding the past two years.
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To my major advisor, Dr James Hampton, Ph.D., thank you for all your assistance and guidance throughout the past year. To Jolene Miller, Scholarly Project Coordinator, thank you for your help in my research and with the organization of my paper.
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Introduction

Shockwave lithotripsy (SWL) has been used in the United States since 1982 to effectively treat nephrolithiasis. The procedure was thought to be relatively benign with few complications other than bruising on the back where the shock wave entered and hematuria. One complication, often viewed as minor, was the development of acute pancreatitis; however no long term follow up studies had been done (Krysiewicz, 1992). In May 2006, The Journal of Urology published a 19 year follow-up study on patients who received shockwave lithotripsy in 1985 at the Mayo Clinic. This study showed that patients who received SWL had an increased risk of developing diabetes mellitus as compared to controls. When multivariate analysis was used to take change in body mass index (BMI = wt (kg)/ ht(m2)) into consideration, the relative risk increase was 3.75 (Krambeck et al., 2006). The development of diabetes is thought to be due to pancreatitis (discussion to follow) which, as mentioned above, was thought to mostly be a minor complication. (Krambeck et al.). If future studies uphold the results of Krambeck et al, pancreatitis as a complication of SWL may have to be viewed as potentially having more serious long term consequences.
Lithotripsy

The effect of shock waves on aircraft was being studied in the late 1960’s by Dornier Systems in West Germany. Part of the study included the effects of the shock waves on humans. Through tissue and animal studies, several important observations were made. These included: 1) shock waves can travel through water and tissues without loss of energy; 2) the shock waves traveling through water could be focused; 3) other than the lungs, tissues tolerated shock waves without damaging effects; 4) brittle materials were fractured by the stress of the shock waves. In 1974, a grant was awarded to Egbert Schmiedt at the University of Munich where he began using these principles to produce a safe and reproducible method of treating kidney stones. On February 8, 1980, the first shock wave destruction of a kidney stone in a human patient took place (deVere White, Ralph W. Palmer, & M., 1987).

The shock waves used to break the stone are generated in water. By placing a pair of electrodes in the water and creating a spark between them, a small amount of water is vaporized. The vapor expands and then as it cools it condenses and collapses onto itself. As it collapses it creates an expanding shock wave. The energy of this shock wave is then focused, using a brass bowl, to a point in space called F2. F2 is the point where the energy of the shock wave is at its highest density (Chaussy et al., 1982; Marberger, Fitzpatrick, Jenkins, & Pak, 1991). Focusing of the shock wave onto the stone is done through the use of two x-rays. The patient is positioned using the x-rays as a guide to assure that the stone is aligned with the focal point (F2) of the shock wave (Fuchs, Rassweiler, & Eisenberger, 1985). To prevent possible interference with the electric conduction system of the heart, and possible development of arrhythmias, the shock waves need to be transmitted during the refractory phase of the cardiac cycle. This is done by
initiating the transmission during the R wave of the patients EKG (Chaussy et al.; Marberger, et al.).

The first lithotripters used a pair of electrodes in water to create the shock wave. With these lithotripters the patient was submerged in a water bath, because water was needed to conduct the shock wave. The patient also had to be under general anesthesia due to the pain caused by the shock wave (Marberger, et al., 1991). Newer model lithotripters employ water filled units that contain the shock wave generator. This unit is then placed directly on the patient using ultrasound jelly as a conduction medium and eliminating the need for submerging the patient in a water bath. The method of shock wave generation has also changed. Electromagnetic generators create high energy sound waves that are focused and used to shatter the stone (Sheir, Madbouly, & Elsobky, 2003). These newer innovations have decreased discomfort for the patient and general anesthesia has been replaced with mild sedation during the treatment. However the effectiveness of stone disintegration has also decreased and the rate of repeat treatment has increased (Gerber, Studer, & Danuser, 2005).
Types of Stones

There are three main types of nephrolithiasis: calcium oxalate stones, uric acid stones, and struvite stones. Calcium oxalate stones make up the majority of nephrolithiasis, about 77%. Uric acid stones make up about 11% of all kidney stones. Struvite stones make up about 8% (Grases, Costa-Bauza, & Prieto, 2006). Calcium oxalate stones are caused by four main factors: hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia. Hypercalciuria is due to either the increased absorption of calcium in the small intestines, hyperparathyroidism which leads to increased reabsorption of bone, or to the inability of the renal tubual to reabsorb filtered calcium. Hyperuricosuria is due to dietary excess of uric acid. Hyperoxaluria is due to the increased absorption of oxalate by the small intestines. Citrate is able to bind to calcium in solution and prevent it from forming stones. For this reason hypocitraturia can lead to calcium stone formation (Stoller & Carroll, 2006).

Diet modifications can help to prevent calcium oxalate stones. By decreasing the amount of oxalate containing foods consumed, the amount of oxalate available for stone formation is reduced. Foods such as nuts, spinach, chocolate, green tea, and those containing soybean seeds are all high in oxalate. Increasing foods such as legumes and cereal brans increase the amount of phytate in the body, which in turn can inhibit calcium salt crystallization. An increase in the amount of citrate consumed, commonly done through potassium citrate supplements, can also inhibit the formation of calcium containing stones. Increasing fluid intake, particularly water, can decrease the concentrations of calcium and oxalate in the urine and inhibit stone formation (Grases, et al. 2006).

Uric acid nephrolithiasis are typically found in urine with a pH less than 5.5. By increasing the pH of the urine above 6.5 many large uric acid stones can be dissolved. This is
most commonly done by supplementing the diet with potassium citrate. Other contributing factors can include rapid weight loss, medications and malignancy. The medication allopurinol can be used to reduce the amount of stone formation if hyperuricemia is present (Tierney, McPhee, & Papadakis, 2006).

Struvite stones are common in women with recurrent urinary tract infections that are intractable to appropriate antibiotics. The stones are due to the urease produced by the infecting bacterium. These include *proteus, pseudomonas, providencia, klebsiella, staphylococcus*, and *mycoplasma* (Tierney, et al. 2006).

Stones greater than 8mm in diameter qualify for evaluation for shock wave lithotripsy treatment (Cupisti et al., 1996). Patients with stones larger than 3 cm in diameter may need to undergo additional procedures to achieve urinary passage of all the fragments (Krysiewicz, 1992). Calcium oxalate stones less than 2 cm diameter can be readily pulverized by shock wave lithotripsy. Struvite stones also respond well to lithotripsy. However, calcium phosphate stones and cystine stones are resistant to shock wave lithotripsy (Marberger, et al., 1991).
Side Effects of Lithotripsy

Although shock wave lithotripsy has largely been considered a benign treatment, over the last several years many rare, but serious, side effects have been discovered. The following are rare, but potentially dire side effects of SWL.

One of the first things that should be addressed is the pain associated with shock wave lithotripsy. In the early 1980’s when the HM-3 lithotripter was first being used, patients had to be put under general anesthesia because of the pain associated with the shock wave. As the lithotripters evolved so did the method of pain control during the procedure. Pain control evolved from general anesthesia, to regional anesthesia to, in some cases, none at all. Recently, a study was done to compare on a 10 point scale the amount of pain felt on five different procedures done without anesthesia (SWL, cystoscopy, retrograde ureteral stenting, retrograde pyelography, and ureteroscopic lithotripsy). Of the five, SWL was rated as the most painful by the patients. The patients rated the pain as a 6.62/10 (Jeong, Park, Kwak, Oh, & Kim, 2005).

Complications of shock wave lithotripsy (SWL) include bruising of the back of the patient where the shock waves enter. Although very rare, hepatitis can occur. Hematochezia can also occur due to damage to the mucosal lining of the colon (Krysiewicz, 1992). Gross hematuria for the first 24 hours affects nearly everyone receiving lithotripsy (Marberger, et al., 1991). This is most likely due to tissue and blood vessel damage in the kidney caused by a phenomenon known as cavitation. Cavitation is damage caused by “microbubbles” that are generated during the propagation of the shock wave (Delius, Enders, Xuan, Liebich, & Brendel, 1988; Delius et al., 1988; Krysiewicz, 1992). The energy created by the cavitation has been shown to be powerful enough to create holes in thin pieces of metal foil (Coleman, Saunders, Crum, & Dyson, 1987). It is this energy that is used to create the fragmentation of the stone. When the
bubbles are formed inside blood vessels, rapid expansion of the bubbles can lead to dilation and rupture of the vessel wall. Recent evidence also suggests that the collapse of an existing bubble may cause many smaller bubbles to form. These bubbles in turn can expand and cause additional damage with each successive shock wave. Additionally, it has been shown that bubbles in large vessels interacting with shock waves can perforate the vessel (Zhong, Zhou, & Zhu, 2001).

A recent article in the Journal of Emergency Medicine discussed the case of an elderly man presenting to the emergency department, with the complaint of right flank pain, three hours after having shockwave lithotripsy to his right kidney. A subcapsular hematoma on his right kidney was found by CT scan. As many as 30% of patients may develop subcapsular hematomas post treatment, but it is suggested that less than one percent are associated with pain or significant bleeding. One of the biggest risk factors for a bleed is hypertension. Hypertension induces atherosclerotic changes in the vessel walls, resulting in the loss of tensile strength. Without this tensile strength, the vessel walls are more susceptible to damage by the shock waves. Hypertension can increase the risk of renal hematomas to 2.7% from less than 0.6% (Sherman & Dogon, 2006).

Using computerized tomography and magnetic resonance imaging, other studies have shown that hematomas do occur in 20-25% of patients. These studies also confirm that less than one percent of patients present symptomatically post treatment with ultrasonographic assessable hematomas. Routine screening of patients post treatment showed that 4.1% had hematomas detectable by ultrasound. Patient age is a risk factor for the development of hematomas. As the patients’ age increased, so did their risk of developing a hematoma. Although it was not statistically significant, patients treated for caliceal stones were twice as likely to develop
hematomas when compared with patients treated for renal pelvic stones (Dhar, Thorton, Karafa, & Streem, 2004).

A case in Germany reported the need for removal of the kidney after treatment with shock wave lithotripsy for a left sided stone. After the lithotripsy treatment, the patient complained of left flank pain and became increasingly hemodynamically unstable. Hemodynamic instability is a state of hypotension resulting in inadequate organ perfusion. A CT and subsequent surgery revealed that there were multiple lacerations to the kidney and it had to be removed (May, Gunia, Helke, Seehafer, & Hoschke, 2004).

When treated with shock waves, stones break into smaller pieces that can then be easily passed in the urine by the patient. If one of the pieces is not small enough to pass it can cause an obstruction and can cause serious problems. The effective renal plasma flow (ERPF) has been shown to decrease post treatment, as has the glomerulus filtration rate (GFR). The decrease in GFR and ERPF has been shown to be transient. However, when associated with obstruction, it has a chronic effect on renal function, and causes permanent parenchymal damage. Treatment of an obstruction after lithotripsy must occur quickly to limit the amount of permanent damage (Sheir & Gad, 2003).

Damage to the parenchyma has been noted even in the absence of obstruction. There have been several cases of acute renal failure (ARF) following SWL unilaterally. One patient in Italy developed oligourea two days post treatment with SWL. His serum creatinine had risen to over 9 mg/dl. Ultrasound revealed no hematomas to the kidneys. Within four weeks his kidney function returned to normal, indicating a diagnosis of acute tubular necrosis (ATN). It is postulated that SWL may reduce renal blood flow in both kidneys, not only the one being treated. With this in mind, renal ischemia can cause tubular damage (Liguori et al., 2004).
Renal injury not associated with renal failure occurs in 63-85% of all patients undergoing SWL, including 30% of patients who have a reduction in plasma flow following treatment. This damage is caused by inflammation set in motion by parenchymal damage from the SWL. The inflammation leads to scar formation and permanent kidney damage. One small scale study showed chronic changes due to scarring of the kidney in seven of twelve patients followed. Scarring leads to the destruction of the glomerular capillaries and thus loss of function of the kidney (Evan, Willis, Lingeman, & McAteer, 1998).

Although rare, gastrointestinal injury caused by shockwave lithotripsy is a severe side effect. One study proposed that as many as 80% of patients undergoing shockwave lithotripsy develop gastric and duodenal erosions due to the treatment. One case involved a 44 year old man who, after undergoing SWL, presented in the emergency department with right lower quadrant pain. A CT of the abdomen showed free air. A laparoscopic procedure showed a perforation in the cecum. A review of literature by Maker et al showed that only 62 of 3,423 patients who underwent SWL had documented gastrointestinal complications. Of the 62, only 9 had injuries that demanded surgical intervention. Small bowel perforations were present in six of the nine while the other three had colon perforations. There was one case in the review in which the patient developed an ureterocolic fistula post treatment with shock wave lithotripsy. Pancreatic hematomas and peripancreatic abscesses were also sited as complications post SWL. The mechanism for the damage is not known but the theory of cavitation was proposed as the most plausible. The mechanical damage due to micro-bubble cavitation has been projected as a possible mechanism; however, chemical damage due to cavitation is also a possible mechanism. The cavitation has been shown to generate free radicals, highly reactive substances which can cause cell injury and cell death. Lastly, the position of the patient during the procedure has been
used to explain some of the gastrointestinal damage. Patients placed in the prone position have shown a high incidence of intestinal perforations (Maker & Layke, 2004).

Patients with a stone in the upper portion of the left kidney and enlarged left spleen may need special attention. A recent case in Germany involved the rupture of a patient’s spleen while undergoing SWL. Hours after undergoing SWL the patient presented to the emergency department with low blood pressure, tachycardia, and low hemoglobin levels. A splenectomy was performed after a CT scan revealed a subcapsular rupture of the patient’s spleen (Kastelan et al., 2005).

A 2001 study showed that there is a decline in sperm density, motility and vitality following SWL for distal ureteral stones. The study compared healthy men who underwent SWL for distal ureteral stones as compared to healthy men who underwent SWL for more proximal stones. The impairment, however, was only transient and values returned to normal within 12 weeks (Martinez Portillo et al., 2001).

Lung tissue is very susceptible to damage by SWL and care is taken to prevent the shock waves from passing through lung tissue. However, there are cases reported where lung parenchyma is damaged by SWL. The lung tissue is very sensitive to shock waves, as are the capillary endothelial cells. The passage of a shock wave through lung tissue causes damage to both types of cells, resulting in hemoptysis. The damage is often minimal, but cases of death have been reported (Tiede, Lumpkin, Wass, & Long, 2003).

In 2001, Kochanski et al performed experiments on the effect of shock waves on DNA. Although they were unable to definitively state a mechanism of damage, they reported that damage was done to DNA in the path of shock waves from an electromagnetic lithotripter. The
electromagnetic lithotripter was chosen to prevent damage to the DNA by light from a spark-gap lithotripter (Kochanski, Mejnartowicz, Latos-Bielenska, Etienne, & Filipczynski, 2001).

Hypertension is a possible side effect of SWL, however, whether or not it is truly a complication relating to SWL or not is still being debated. In 1987, Lingeman et al and Newman et al independently published studies showing an increase in the prevalence of hypertension following SWL (Lingeman & Kulb, 1987; Newman, Williams, Kaude, Peterson, & Thomas, 1987). Lingeman’s study showed new onset hypertension in over eight percent of patients treated with SWL, and over 15% of patients had a diastolic blood pressure increase. He reported that the increase in diastolic blood pressure occurred regardless of side of treatment, whether it was unilateral or bilateral treatment, and regardless of the number of shocks delivered during treatment. It was theorized that parenchymal damage caused focal scaring in the kidney; which caused an increase in renin release which in turn caused an increase in blood pressure (Lingeman & Kulb).

A study published in The Journal of Urology in 1992 contradicted Lingeman’s results. They stated that the number of patients who had a decrease in blood pressure was greater than the number of patients that showed an increase in blood pressure. The newer study also showed that although there was an overall increase in the diastolic blood pressure of patients, it was not statistically significant. This study did however show that there was a statistically significant increase in diastolic blood pressure in patients related to the number of shocks received during treatment. The patients who received a large number of shocks, tended toward having an increase in their diastolic blood pressure. The authors conceded that the results were with a small number of patients and that further studies would need to be done with larger groups of patients (Yokoyama et al., 1992).
In 1998, a study conducted at the University of Toronto was published in The Journal of Urology. This study followed 154 patients who were randomized into a control group who were observed and a treatment group who underwent SWL for the treatment of renal stones. The groups were then followed on a regular basis for two years. During the two years, two patients in both the control group and the treated group developed new onset hypertension. This study showed no change in blood pressure from baseline for either the control group or the group undergoing SWL (Jewett et al., 1998).

A 2000 British study confirmed the results from the study from the University of Toronto in 1998. The British study involved 228 patients who were randomized into either a control group (115 patients) or a treatment group (113 patients). The patients were followed for up to five years with the average length of follow up being 2.2 years. The study concluded that there was no statistically significant increase in blood pressure after treatment with shock wave lithotripsy. The authors did suggest however, that the changes may not show up as meaningful changes in blood pressure. They proposed that the changes may show up as an increase in morbidity and mortality from hypertension related causes such as stroke and heart disease (Elves et al., 2000).

In contrast to the previous two studies which showed no increase in the incidence of hypertension after treatment with SWL, a study published in The Journal of Urology in 2006 showed an increase in hypertension in patients following treatment with SWL. This study followed patients 19 years after treatment with SWL for renal and proximal ureteral stones. In the study, questionnaires were mailed to 578 patients (58.9% responded) who were treated with SWL in 1985. These patients were matched with a control group who were treated non-surgically for stones. The rate of hypertension in the treated group was nearly 1.5 times higher
than in the non-treated group. The authors noted that the largest increase was within the group that underwent bilateral SWL (Krambeck et al., 2006).

One side effect of SWL that is not being debated is the development of pancreatitis following SWL. Several cases of acute pancreatitis have been documented after treatment with SWL (Abe, Nisimura, Osawa, Miura, & Oka, 2000; Hassan & Zietlow, 2002; Hung, Chen, Jan, & Chen, 2000; Karakayali et al., 2006). One proposed mechanism for the pancreatic damage is adhesions caused by the SWL (Abe, et al.). Another proposed mechanism for the development of pancreatitis is cavitation (Hassan & Zietlow,; Hung, Chen, Jan, & Chen, 2000; Karakayali et al., 2006). That is, the same forces used to break up the stone and that has been linked to hematuria post-treatment with SWL, is also causing the damage to the pancreas. Damage to the pancreas could have long term consequences for the patient. It is suggested that diabetes could be a long term complication to SWL. The mechanism for the development of diabetes is possibly through the damage done to the pancreas from recurrent bouts of pancreatitis.
Pancreatitis

Pancreatitis is an inflammation of the pancreas due to the autodigestion of the pancreas by activated pancreatic enzymes. There are acute and chronic types. The acute type has both a mild and a more serious form. The more serious form is known as acute hemorrhagic pancreatitis. Etiologies of pancreatitis include gallstones, alcohol, and hypertriglyceridemia. There are three phases to acute pancreatitis. First is the activation of the digestive enzymes while they are still in the pancreas and damage to the acinar cells. Acinar cells comprise greater than 90% of the exocrine cells of the pancreas and are responsible for the production of proteases, lipases, and amylases. The second phase involves the sequestration of neutrophils in the pancreas which is the cause of the inflammation seen. The third phase is due to the proteolytic effects of the pancreatic enzymes on other organs leading to such conditions as systemic inflammatory response syndrome (SIRS) and acute respiratory distress syndrome (ARDS) (Greenberger, 2005).

Gall stones are regarded as the most common cause of acute pancreatitis. Small stones, consisting of mostly cholesterol, migrate from the gall bladder into the pancreatic duct and create an obstruction (Yan & Li, 2006). Experiments have shown that obstruction of the pancreatic duct changes the pancreatic response to calcium. High intracellular calcium concentrations have been associated with the premature activation of the pancreatic digestive enzymes. The activated enzymes are then able to cause damage to the pancreas (Halangk & Lerch, 2004).

Hypertriglyceridemia is another well documented cause of acute pancreatitis. A triglyceride level of 1,000 to 2,000 mg/dL (values less than 250 mg/dL is considered normal) is considered a risk factor for developing pancreatitis (Iskandar & Olive, 2004). A patient with pancreatitis and triglyceride levels greater than 1,000 mg/dL with all other causes of pancreatitis
excluded is considered to have pancreatitis due to hypertriglyceridemia (Navarro et al., 2004). The pancreatitis occurs due to the irritation of the acinar cells as well as the capillaries by free fatty acids (Fortson, Freedman, & Webster, 1995).

Chronic pancreatitis is a disease state in which the glandular cells of the pancreas are replaced by scar tissue. The scar tissue forms due to repeated incidents of inflammation. Recurrent cases of acute pancreatitis can lead to chronic pancreatitis. Within 25 years of the development of chronic pancreatitis, over 80% of patients develop diabetes (Tierney, McPhee, & Papadakis, 2006).

Alcohol abuse has long been associated with chronic pancreatitis (Apte & Wilson, 2003; Fox, 2006). Recent evidence indicates that acute pancreatitis may commonly be due to alcohol use (Apte & Wilson; Hanck & Whitcomb, 2004; Nordback, Pelli, Lappalainen-Lehto, & Sand, 2005). In 2005, Nordback et al found that the first symptoms of acute pancreatitis often came after the cessation of alcohol following long term use (Nordback, Pelli, Lappalainen-Lehto, & Sand, 2005). It has been proposed that the alcohol does not have a direct causative effect in the development of pancreatitis; however it may just lower the threshold of the disease to some other contributory agent. The damage to the pancreas may also be due to the toxic effects of the alcohol on the acinar cells. These cells are responsible for the production of the pancreatic digestive enzymes. In animal studies, the acinar cells have had mitochondrial damage associated with alcohol use. With the damage to the mitochondria, and the subsequent decrease in ATP the acinar cells would have difficulty regulating intracellular calcium (Hanck & Whitcomb).

Chronic pancreatitis is due to the destruction of the pancreas, often after several attacks of acute pancreatitis. Patients with chronic pancreatitis have less than 10% of the exocrine function of their pancreas intact (Greenberger, 2005). An increased risk of pancreatic cancer is
associated with chronic pancreatitis due to unwanted cellular proliferation. Up to 80% of the cases of chronic pancreatitis are associated with heavy alcohol use. However, a predisposition to chronic pancreatitis is believed to exist to the fact that only 5% to 10% of those who abuse alcohol develop the disease. There is also a hereditary link to pancreatitis with 80% of the patients inheriting the gene developing chronic pancreatitis. The prevalence of chronic pancreatitis is less than 5%. It does however have an association with obesity, insulin resistance and type 2 diabetes mellitus which are all increasing, therefore one can expect an increase in the rate of chronic pancreatitis (Fox, 2006).

Current research has shown that smoking causes an increased risk for pancreatitis. It has been shown that prolonged exposure to nicotine can cause an increase in the accumulation of the digestive enzymes trypsinogen and chymotrypsinogen (Wittel et al., 2006). Laboratory studies have also shown that nicotine exposure can lead to high intracellular calcium levels (Maisonneuve et al., 2005). As discussed earlier, high intracellular calcium levels can lead to activation of the digestive enzymes that are now at higher than normal levels. Unfortunately, for some the first symptom of pancreatitis is the development of pancreatic insufficiencies such as steatorrhea or diabetes mellitus (Apte & Wilson, 2003). As eluded to earlier, a study published in 2006 found that diabetes could be a long term complication from SWL. Following is a brief description of the two types of diabetes as well as commonly accepted etiologies of both types.
Diabetes Mellitus

Diabetes mellitus is classically described as two types. Type 1 is the inability of the pancreas to make insulin while type 2 is explained as a triad of insulin resistance, impaired insulin secretion, and increased glucose production. Type 1 has two subtypes. Type 1 A is due to the autoimmune destruction of the insulin producing beta cells of the pancreas. In type 1B diabetes mellitus, there are no serologic markers indicating autoimmune destruction of the beta cells; however, the beta cells are destroyed (Powers, 2005). The etiology of type 1 diabetes is thought to be the combination of genetics and some environmental trigger (Gillespie, 2006; E. Hathout, W. Beeson, M. Ischander, R. Rao, & J. Mace, 2006; E. H. Hathout, W. L. Beeson, M. Ischander, R. Rao, & J. W. Mace, 2006; Hirschhorn, 2003; Knip, 2003).

The genetic etiology of type 1 diabetes has several components. One of the most studied is known as the HLA locus on chromosome 6 (E. H. Hathout, et al., 2006). There are at least 15 other loci that can be attributed to causing type 1 diabetes. There are also two genes associated with t-cell activation which are being studied as possible factors involved in the autoimmune response seen in type 1 diabetes (Gillespie, 2006). Twin studies have also provided information regarding the genetic component to type 1 diabetes. Monozygotic twins are more likely to both develop type 1 diabetes as compared to dizygotic twins (Hirschhorn, 2003).

Twin studies have also been used as evidence in the fact that there is some environmental trigger for the susceptible population to develop diabetes. This was shown as only a small proportion of the susceptible population went on to develop the disease (E. H. Hathout, et al., 2006; Knip, 2003). The presence of an environmental trigger is also evident when comparing dizygotic twins with other siblings. Dizygotic twins show a higher rate of diabetes than do siblings. This can be attributed to the common environment shared by twins (Hirschhorn, 2003).
Variability in the incidence of type 1 diabetes in genetically similar populations separated by geography also lends credence to the theory of an environmental trigger (Hirschhorn). Kathleen Gillespie notes that currently there is a worldwide increase in the incidence of type 1 diabetes of about 3% per year. She contributes this rapid rise to some environmental trigger on those having the susceptible genes (Gillespie, 2006).

Many factors have been found that may be the environmental trigger for type 1 diabetes. Air pollution was studied and it was found that people exposed to ozone and sulfate had a higher rate of type 1 diabetes. Passive smoking was more frequent in children with diabetes (30%) than those without (10%). It has been theorized that the damage done to the beta cells by these pollutants is due to free radical destruction (Hathout, et al., 2006).

Infections have been sited as triggers for diabetes in the susceptible. One infection that has been identified is enteroviruses, which have been shown to induce diabetes in experimental animals. Studies have shown that there is an increased risk for developing diabetes for a child whose mother had an enterovirus infection during pregnancy. Congenital rubella infections have also been sited as a cause of diabetes (Knip, 2003).

Dietary factors may also be the causative factor in the initiation of the destruction of the beta cells. Finnish research has shown that a large amount of cow’s milk in childhood was associated with a higher rate of type 1 diabetes. The foundation for the research into the relationship between consumption of cow’s milk and diabetes centers around two concepts. The first is the difference in the proteins that make up cow’s milk as compared to the proteins that make up human milk. The second is the difference in the amino acid sequence of the bovine insulin that is present in the cow’s milk and the amino acid sequence of human insulin. A Swedish study has linked zinc deficiency and type 1 diabetes (Knip, 2003).
As the search for the environmental triggers for type 1 diabetes continues, some protective factors have emerged. A Finnish study found that even sporadic supplementation of vitamin D during infancy can be protective against the development of type 1 diabetes (Knip, 2003). Children who attend daycare and children who are breastfed in infancy have been shown to have a lower relative risk for developing type 1 diabetes (Hathout, et al., 2006).

The triad that describes type 2 diabetes is a summary of interlinked mechanisms. Insulin resistance is the inability of the cells, especially the skeletal muscle cells and the hepatic cells, to recognize insulin. The mechanism is unknown; however, it is known that the number of insulin receptors on the skeletal muscle cells decrease. This decrease in receptors is believed to be due to the hyperinsulinemia state and the cells down regulation reaction to this state. The defect in insulin resistance is more likely related to the post receptor pathway. The impaired insulin secretion is due to the pancreas’ inability to continue to make the high levels of insulin needed to get cellular response to the insulin. This is because the cells have become resistant to the insulin. The third leg of the triad is increased gluconeogenesis. This is due to the hepatic cell’s insulin resistance, and the liver cells inability to recognize the hyperinsulinemia and therefore the hyperglycemic state on the body. The hepatic cells then begin gluconeogenesis to compensate for their perceived low blood sugar state (Powers, 2005).

The etiology of type 2 diabetes mellitus is not completely understood. There are many risk factors that are associated with the development of type 2 diabetes. The relationship of weight and diabetes has been well publicized. A higher risk of diabetes exists amongst those who are overweight as adults. Losing weight during adulthood has been shown to reduce the risk of developing diabetes, but not to the same level as those who have never been overweight (Jeffreys et al., 2006). A Danish study suggests that it is not the overall attained weight that increase the
risk of developing diabetes, rather it is the amount of weight gained after the age of 20 (Black et al., 2005). Rather than looking at a persons’ BMI, an Iranian study suggests that it is better to compare ones waist/ height ratio to evaluate their risk of developing type 2 diabetes (Hadaegh, Zabetian, & H. Azizi, 2006).

Smoking increases a person’s risk of developing type 2 diabetes independent of other risk factors. The weight gain associated with stopping smoking does not increase one’s risk of diabetes as much as stopping smoking lowers the risk (Patja et al., 2005).

Physical activity level is also associated with the development of type 2 diabetes mellitus. An increase in physical activity can decrease the risk of developing type 2 diabetes. This protective effect can be seen regardless of BMI (Hu et al., 2004). Hu et al observed that activity levels were lower among those who were overweight or obese (Hu et al., 2004). In a study to determine the effect of lifestyle on the development of diabetes, a group of patients with impaired glucose tolerance were counseled on weight loss and increasing physical activity. This group of patients had an overall reduction in the incidence of the development of diabetes of 58% as compared to a control group (Tuomilehto, Lindstrom, Eriksson, & Valle, 2001). Other characteristics that have been associated with the development of diabetes are a low education level and a high systolic blood pressure (Bener, Zirie, & Al-Rikabi, 2005).
Linking Lithotripsy with Diabetes Mellitus

In 2004, The Mayo Clinic in Rochester, Minnesota completed a 19-year follow up on the 630 patients that had had SWL in 1985 at their facility. It was determined that 578 patients were still alive at the time. A survey was mailed to them, and 58.9% responded. Patients were identified who had preexisting renal insufficiency, preexisting obesity (BMI greater than 30), or preexisting hypertension. A control group was also established. The control group was established by reviewing charts of patients with nephrolithiasis who were managed non-surgically. The control group was matched to the experimental group based on age (± 5 years), sex, and year of presentation (± 1 year) (Krambeck et al., 2006).

The experimental group included 218 females and 404 males. Bilateral stones were found in 57 cases, left sided stones in 384 cases and right sided stones in 295 cases. Eight of the patients had diabetes prior to undergoing SWL. Postoperative complications were reported by 40 of the patients that responded to the survey. The development of complications was associated with the number of shocks, voltage, average intensity, total intensity, the number of locations treated and the number of separate treatments (Krambeck et al., 2006).

The patients treated with SWL who responded to the survey were much more likely to have developed diabetes than their counterparts in the control group. However, it was noted by the researchers that there was a significant difference in obesity (BMI>30) for the experimental group as compared to the control group (p<0.001). The SWL group had a greater percentage of obese individuals. When BMI was taken into consideration, the risk for developing diabetes mellitus in the SWL group was 3.75% (p<0.003). It was found that the increased risk existed regardless of which side the treatment took place (Krambeck et al., 2006).
The researchers hypothesized that the increased risk of developing diabetes in the SWL was due to damage to the pancreatic islet cells. The HM-3 lithotripter is known to have the pancreas in its shock wave path regardless of the side of treatment. The researchers also noted that F2 in the HM-3 has a larger cross section than the newer machines. They also found that obese patients were more likely to develop the disease than the non obese counterparts after treatment with SWL. Overall it was noted that diabetes development was associated with the total intensity and the number of shocks received (Krambeck et al., 2006).

The study done by the Mayo Clinic followed patients who were treated with the Dornier HM-3 lithotripter (HM-3). The HM-3 was the first lithotripter, and although it revolutionized the way patients were treated, it did have some shortcomings which were eliminated by later machines. The first problem with the HM-3 was that the focal point of the shock-wave energy (F2) was not as focused as the machines of today. When using the HM-3 lithotripter, F2 just needed to be in the vicinity of the stone to work. The newest lithotripters use computers to center the more focused F2 onto the stone; however this was not the case with the HM-3. When a patient was being treated with the HM-3, AP and lateral radiographs were obtained and then the lithotripter was placed at an oblique angle to the patient and the technician made the best approximation possible to make sure the stone was centered at F2. Taking into consideration these observations, it is reasonable to see how a patient may suffer damage to other tissues when being treated with the HM-3 (B. Balduf, personal communication, November 11, 2006).

Short term studies could now be done to follow patients receiving lithotripsy from one of the newer machines. Serum amylase and lipase levels could be measured post-treatment revealing if any damage is being done to the pancreas. Future long term studies could be
conducted to determine the risk of the development of diabetes following treatment with one of the newer computer controlled lithotripters.

Lithotripsy is, and will continue to be, a treatment modality for the treatment of nephrolithiasis. It is important when a physician assistant (PA) is counseling a patient about treatment options for their kidney stones, that it is not forgotten that there can be serious side effects. Although lithotripsy has historically been considered a benign treatment, there are rare but severe side effects. Also, the long term side effects of treatment with lithotripsy are just coming to light. Diabetes and hypertension are two very serious diseases, and if future studies confirm the results Krambeck et al. patients need to be made aware.
References


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Abstract

In 2006, The Journal of Urology published a 19 year follow-up study on patients who received shockwave lithotripsy in 1985. This article stated that research showed a correlation between shockwave lithotripsy and diabetes mellitus.

Google-scholar, Pubmed, and Medline were used to find scientific articles related to lithotripsy, pancreatitis, and diabetes.

Results of the literature review were that side effects to lithotripsy are rare and usually mild in nature; however, there are occasionally more serious side effects. One of the more serious side effects is pancreatitis. It is known that recurrent pancreatitis can lead to diabetes mellitus. The link between lithotripsy and diabetes mellitus was hypothesized to be due to damage often done to the pancreas during the procedure. In conclusion, one research paper published in 2006 found a link between lithotripsy and diabetes; however more research in this area is needed.