Sodium, kidney and renal sodium retention

Yan Yang *, Hongbao Ma *, **

* Brookdale University Hospital and Medical Center, New York 11212, USA,
youngjenny2008@yahoo.com; 1-347-321-7172
** Bioengineering Department, Zhengzhou University, Zhengzhou, Henan 450001, China;
ma8080@gmail.com; 01186-137-8342-5354

Abstract: The tight regulation of the body's sodium and chloride concentrations is so important that multiple mechanisms work in concert to control them, and a minimal amount of salt is required for survival. Sodium (Na^+) and chloride (Cl^-) are the principal ions in the extracellular fluid, especially in blood plasma. Sodium retention is the most common renal abnormality of cirrhosis and eventually leads to the formation of ascites. The arterial vasodilatation, mainly splanchnic, that occurs during liver cirrhosis is a major factor in the pathogenesis of renal sodium and water retention. The arterial vasodilatation and the subsequent hypotension stimulate a baroreceptor-mediated neurohormonal vasoconstrictor and antinatriuretic response in an attempt to compensate the relative underfilling of the circulation. Renal sodium and water retention and plasma volume expansion have been shown to precede ascites formation in experimental cirrhosis.
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Introduction

Sodium is a metallic element with symbol Na, atomic number 11 and atomic weight 23. It is a soft, silvery-white, highly reactive metal and is a member of the alkali metals. It has only one stable isotope, ^{23}Na.

Elemental sodium was first isolated by Sir Humphry Davy in 1806 by passing an electric current through molten sodium hydroxide. Elemental sodium does not occur naturally on Earth, but quickly oxidizes in air and is violently reactive with water, so it must be stored in an inert medium, such as a liquid hydrocarbon. The free metal is used for some chemical synthesis, analysis, and heat transfer applications.

Sodium ion is soluble in water in nearly all of its compounds, and is thus present in great quantities in the Earth's oceans and other stagnant bodies of water. In these bodies it is mostly counterbalanced by the chloride ion, causing evaporated ocean water solids to consist mostly of sodium chloride, or common table salt. Sodium ion is also a component of many minerals.

Sodium is an essential element for all animal life and for some plant species. In animals, sodium ions are used in opposition to potassium ions, to allow the organism to build up an electrostatic charge on cell membranes, and thus allow transmission of nerve impulses when the charge is allowed to dissipate by a moving wave of voltage change. Sodium is thus classified as a “dietary inorganic macro-mineral” for animals. Sodium's relative rarity on land is due to its solubility in water, thus causing it to be leached into bodies of long-standing water by rainfall. Such is its relatively large requirement in animals, in contrast to its relative scarcity in many inland soils, that herbivorous land animals have developed a special taste receptor for sodium ion.

Sodium transport, the kidney function that regulates the level of salt in the kidney and bloodstream and, ultimately, blood pressure, may be intimately related to some of the same genes that have been implicated in the unchecked cellular growth of cancer.

The nephrotic syndrome is a frequent clinical condition characterized by fluid and salt retention. Although several theories have been put forward to explain the salt-retaining status, recent data have confirmed previous renal micropuncture observations indicating that the distal nephron is the site for increased salt reabsorption, eventually leading to sodium retention. The epithelial sodium channel (ENaC) and basolateral Na^+, K^+-ATPase as the main transport proteins responsible for increased transepithelial sodium reabsorption in various forms of experimental nephrotic syndrome. Although the fine-tuning for the up-regulation of these transporters has not been so far elucidated, it is clear from clinical studies that the use of amiloride, a selective, dose-dependent ENaC inhibitor, is an appropriate tool to reduce distal sodium reabsorption and thus to offset edema formation (Zacchia et al. 2008).

The pathophysiology of sodium and water retention in heart failure is characterized by a complex interplay of hemodynamic and neurohumoral factors. Relative arterial underfilling is

an important signal that triggers heart failure-related sodium and water retention. The response to perceived arterial underfilling is modulated by the level of neurohormonal activation, the degree of renal vasoconstriction, and the extent to which renal perfusion pressure is reduced. Sodium retention can also be exceeded by water retention, with the result being dilutional hyponatremia. Sodium and water retention in heart failure also function to dampen the natriuretic response to diuretic therapy. The attenuated response to diuretics in heart failure is both disease-specific and separately influenced by the rate and extent of diuretic absorption, the rapidity of diuretic tubular delivery, and diuretic-related hypertrophic structural changes that surface in the distal tubule (Sica 2006).

The resultant increase in renal adrenergic activity stimulates the renin-angiotensin-aldosterone system. Although the resultant increase in systemic vascular resistance compensates for the primary arterial underfilling, this activation of the neurohumoral axis results in diminished sodium and water delivery to the renal collecting duct sites of aldosterone, AVP, and natriuretic peptide action. The role of the nonosmotic AVP release in water retention and hypo-osmolality/hyponatremia has been demonstrated in patients and experimental animals by administering nonpeptide, orally active vasopressin V2 receptor antagonists. These agents have been found to increase solute-free water excretion in patients with water-retaining, hyponatremic edema as well as in experimental animals (Schrier 2006).

The nephrotic syndrome (NS) is usually associated with renal sodium retention. Neither the renal site nor the mechanism of this antinatriuresis is known. Since there is much evidence that sodium reabsorption in the proximal tubule varies with pentubular plasma oncotic pressure, one would predict that the reabsorption of sodium in the proximal tubule would be depressed due to hypoproteinemia in the NS and that the site of enhanced reabsorption would be in the distal nephron (Bernard et al. 1978).

In the nephrotic syndrome abnormal sodium and water retention occurs at the kidney level that ultimately causes expansion of interstitial volume and edema. The mechanisms and factors involved remain ill defined. The traditional view has considered hypovolemia, due to urinary protein losses and decreased oncotic pressure, as the afferent stimulus of a complex pathway of responses that come together to enhance reabsorption of sodium and water along the nephron. However, given the fact that only a minority of nephrotic patients have low plasma volume, it has been hypothesized that sodium retention by the kidney is a primary phenomenon occurring in response to intrarenal rather than systemic mechanisms. Experimental evidence is available to support this possibility, and indicates that distal nephron sites are involved in avid sodium retention in the nephrotic syndrome. Several studies have been designed to establish the role of neurohumoral mediators, including the renin-angiotensin-aldosterone axis and sympathetic nervous system. These data suggest that although activation of these systems may contribute to salt retention, they may be minor factors in this process. Recently, attention has focused on atrial natriuretic peptides (ANP), which increase sodium and water excretion in experimental animals and humans. A markedly blunted natriuretic and diuretic response to the systemic infusion of ANP has been reported in the nephrotic syndrome. A defect in the number and affinity of receptor binding sites for the peptide as well as in the level of intracellular cyclic guanosine monophosphate, the second messenger of ANP, has recently been investigated (Perico and Remuzzi 1993).

The most common renal lesion in adults with NS is membranous nephropathy, in which renal function is usually normal at first [14, 151. The animal model which has been studied most extensively is nephrotoxic nephritis, which corresponds more closely to acute proliferative or rapidly progressive glomerulonephritis in man. In this disease, early renal functional impairment is usual. In 1959, Heymann et al [161 described a model of glomerulonephritis in the rat in which the NS developed while normal renal function was maintained. The immunologic features of this model, now referred to as autologous immune complex nephritis (AICN), have been studied extensively [17—201. The gbmerular lesion in AICN is indistinguishable from that in idiopathic membranous nephropathy in humans. This model seemed especially suitable to study renal handling of sodium since it is morphologically identical to a common cause of NS in man, the characteristic features of NS are well-developed, and GFR is normal.

1. Sodium Chloride

Salt is currently mass-produced by evaporation of seawater or brine from other sources, such as brine wells and salt lakes, and by mining rock salt, called halite. In 2002, world production was estimated at 210 million metric tons, the top five producers (in million tonnes) being the United States (40.3), China (32.9), Germany (17.7), India (14.5) and Canada (12.3).

As well as the familiar uses of salt in cooking, salt is used in many applications, from manufacturing pulp and paper, to setting dyes in textiles and fabric,

to producing soaps, detergents, and other bath products. It is the major source of industrial chlorine and sodium hydroxide, and used in almost every industry.

Sodium chloride is sometimes used as a cheap and safe desiccant because it appears to have hygroscopic properties, making salting an effective method of food preservation historically; as it draws water out of bacteria through osmotic pressure preventing them from reproducing and causing food to spoil. Even though more effective desiccants are available, few are safe for humans to ingest.

The classic case of ionic bonding, the sodium chloride molecule forms by the ionization of sodium and chlorine atoms and the attraction of the resulting ions. An atom of sodium has one 3s electron outside a closed shell, and it takes only 5.14 electron volts of energy to remove that electron. The chlorine lacks one electron to fill a shell, and releases 3.62 eV when it acquires that electron. This means that it takes only 1.52 eV of energy to donate one of the sodium electrons to chlorine when they are far apart. When the resultant ions are brought closer together, their electric potential energy becomes more and more negative, reaching -1.52 eV at about 0.94 nm separation. This means that if neutral sodium and chlorine atoms found themselves closer than 0.94 nm, it would be energetically favorable to transfer an electron from Na to Cl and form the ionic bond. The potential diagram above is for gaseous NaCl, and the environment is different in the normal solid state where sodium chloride forms cubical crystals. The ion separation is 0.28 nm, somewhat larger than that in the gaseous state.

The salt sodium chloride is essential for life. The tight regulation of the body's sodium and chloride concentrations is so important that multiple mechanisms work in concert to control them, and a minimal amount of salt is required for survival.

1.1 Function

Sodium (Na^+) and chloride (Cl^-) are the principal ions in the extracellular fluid, especially in blood plasma. As such, they play critical roles in a number of life-sustaining processes. Many micro organisms cannot live in an overly salty environment: water is drawn out of their cells by osmosis. For this reason salt is used to preserve some foods, such as smoked bacon or fish. It can also be used to detach leeches that have attached themselves to feed. It is also used to disinfect wounds.

1.2 Maintenance of membrane potential

Sodium and chloride are electrolytes that contribute to the maintenance of concentration and charge differences across cell membranes. Potassium is the principal positively charged ion (cation) inside of cells, while sodium is the principal cation in extracellular fluid. Potassium concentrations are about 30 times higher inside than outside cells, while sodium concentrations are more than ten times lower inside than outside cells. The concentration differences between potassium and sodium across cell membranes create an electrochemical gradient known as the membrane potential. A cell's membrane potential is maintained by ion pumps in the cell membrane, especially the sodium, potassium-ATPase pumps. These pumps use the energy by ATP to pump sodium out of the cell in exchange for potassium. Their activity has been estimated to account for 20%-40% of the resting energy expenditure in a typical adult. The large proportion of energy dedicated to maintaining sodium/potassium concentration gradients emphasizes the importance of this function in sustaining life. Tight control of cell membrane potential is critical for nerve impulse transmission, muscle contraction, and cardiac function.

1.3 Nutrient absorption and transport

Absorption of sodium in the small intestine plays an important role in the absorption of chloride, amino acids, glucose, and water. Similar mechanisms are involved in the reabsorption of these nutrients after they have been filtered from the blood by the kidneys. Chloride, in the form of hydrochloric acid (HCl), is also an important component of gastric juice, which aids the digestion and absorption of many nutrients.

1.4 Maintenance of blood volume and blood pressure

Because sodium is the primary determinant of extracellular fluid volume, including blood volume, a number of physiological mechanisms that regulate blood volume and blood pressure work by adjusting the body's sodium content. In the circulatory system, pressure receptors (baroreceptors) sense changes in blood pressure and send excitatory or inhibitory signals to the nervous system and/or endocrine glands to affect sodium regulation by the kidneys. In general, sodium retention results in water retention and sodium loss results in water loss. Below are descriptions of two of the many systems that affect blood volume and blood pressure through sodium regulation.

1.4.1 Renin-angiotensin-aldosterone system

In response to a significant decrease in blood volume or pressure, the kidneys release renin into the circulation. Renin is an enzyme that splits a small peptide Angiotensin I from a larger protein angiotensinogen produced by the liver. Angiotensin I is split into a smaller peptide angiotensin II by

angiotensin converting enzyme (ACE), an enzyme present on the inner surface of blood vessels and in the lungs, liver, and kidneys. Angiotensin II stimulates the constriction of small arteries, resulting in increased blood pressure. Angiotensin II is also a potent stimulator of aldosterone synthesis by the adrenal glands. Aldosterone is a steroid hormone that acts on the kidneys to increase the reabsorption of sodium and the excretion of potassium. Retention of sodium by the kidneys increases the retention of water, resulting in increased blood volume and blood pressure.

1.4.2 Anti-diuretic hormone (ADH)

Secretion of anti-diuretic hormone (ADH) by the posterior pituitary gland is stimulated by a significant decrease in blood volume or pressure. ADH acts on the kidneys to increase the reabsorption of water.

1.5 Deficiency

Sodium and chloride deficiency does not generally result from inadequate dietary intake, even in those on very low-salt diets.

1.6 Hyponatremia

Hyponatremia, defined as a serum sodium concentration of less than 136 mM, may result from increased fluid retention (dilutional hyponatremia) or increased sodium loss. Dilutional hyponatremia may be due to inappropriate ADH secretion, which is associated with disorders affecting the central nervous system and with use of certain drugs. In some cases, excessive water intake may also lead to dilutional hyponatremia. Conditions that increase the loss of sodium and chloride include severe or prolonged vomiting or diarrhea, excessive and persistent sweating, the use of some diuretics, and some forms of kidney disease. Symptoms of hyponatremia include headache, nausea, vomiting, muscle cramps, fatigue, disorientation, and fainting. Complications of severe and rapidly developing hyponatremia may include cerebral edema (swelling of the brain), seizures, coma, and brain damage. Acute or severe hyponatremia may be fatal without prompt and appropriate medical treatment.

1.7 Prolonged endurance exercise and hyponatremia

Hyponatremia has recently been recognized as a potential problem in individuals competing in very long endurance exercise events, such as marathons, ultramarathons, and Ironman triathlons. It has been speculated that the use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of exercise-related hyponatremia by impairing water excretion, but firm evidence is presently lacking.

1.8 Adequate intake for sodium and sodium chloride

In 2004, the Food and Nutrition Board of the Institute of Medicine of US established an adequate intake level for sodium and sodium chloride based on the amount needed to replace losses through sweat in moderately active people and to achieve a diet that provides sufficient amounts of other essential nutrients. These recommended intake levels are well below the average dietary intakes of most people in the US (Table 1).

Table 1. Adequate Intake for Sodium and Sodium Chloride

Life Stage	Age	Males and Females Sodium (g/day)	Males and Females Salt (g/day)
Infants	0-6 months	0.12	0.30
Infants	7-12 months	0.37	0.93
Children	1-3 years	1.0	2.5
Children	4-8 years	1.2	3.0
Children	9-13 years	1.5	3.8
Adolescents	14-18 years	1.5	3.8
Adults	19-50 years	1.5	3.8
Adults	51-70 years	1.3	3.3
Adults	71 years and older	1.2	3.0
Pregnancy	14-50 years	1.5	3.8
Breast-feeding	14-50 years	1.5	3.8

2. Disease Prevention

2.1 Gastric cancer

The stomach is part of the digestive system. It is located in the upper abdomen, between the esophagus and the small intestine. Stomach cancer is also called gastric cancer. Epidemiological studies, conducted mainly in Asian countries, indicate that high intakes of salted, smoked, and pickled foods increase the risk of gastric cancer. Although these foods are high in salt, they may also contain carcinogens, such as nitrosamines. Additionally, populations with high intakes of salted foods tend to have low intakes of fruits and vegetables, which are protective against gastric cancer. The risk of developing stomach cancer is increased by chronic inflammation of the stomach and infection by the bacteria, *Helicobacter pylori*. High concentrations of salt may damage the cells lining the stomach, potentially increasing the risk of *H. pylori* infection and cancer-promoting genetic damage. Although there is little evidence that salt itself is a carcinogen, high intakes of certain salted foods, such as salted fish, may increase the risk of gastric cancer in susceptible individuals.

2.2 Osteoporosis

As the thinning of bone tissue and loss of bone density over time, osteoporosis is a multifactorial skeletal disorder in which bone strength is compromised, resulting in an increased risk of fracture. Nutrition is one of many factors contributing to the development and progression of osteoporosis. Increased salt intake has been found to increase urinary excretion of calcium. Osteoporosis is the most common type of bone disease. Calcium is essential for building and maintaining healthy bone. Vitamin D is also needed because it helps your body absorb calcium. Following a healthy, well-balanced diet can help you get these and other important nutrients throughout life. Each 5.8 g of NaCl excreted by the kidneys draws about 24-40 mg of calcium into the urine. Salt intake has been associated with biochemical markers of bone resorption in some studies but not in others. In general, cross-sectional studies have not found an association between sodium intake and bone mineral density.

2.3 Kidney stones

A kidney stone is a solid mass made up of tiny crystals. One or more stones can be in the kidney or ureter at the same time. Most kidney stones contain calcium as a main constituent. Although their cause is often unknown, abnormally elevated urinary calcium increases the risk of developing calcium stones. Increased dietary salt has been found to increase urinary calcium excretion, and this effect may be more pronounced in patients with a history of calcium-containing kidney stones. Clinical studies have shown that salt restriction reduces urinary calcium in individuals with a tendency to form calcium stones, and a five-year randomized trial of two different diets in men with recurrent calcium oxalate stones found that a diet low in salt and animal protein significantly decreased stone recurrence compared to a low calcium diet.

Kidney stones results from stones or renal calculi in the ureter. The stones are solid concretions or calculi formed in the kidneys from dissolved urinary minerals. Nephrolithiasis refers to the condition of having kidney stones. Urolithiasis refers to the condition of having calculi in the urinary tract, which may form or pass into the urinary bladder. Ureterolithiasis is the condition of having a calculus in the ureter, the tube connecting the kidneys and the bladder. The term bladder stones usually applies to urolithiasis of the bladder in non-human animals such as dogs and cats. Kidney stones typically leave the body by passage in the urine stream, and many stones are formed and passed without causing symptoms. If stones grow to sufficient size before passage on the order of at least 2-3 mm they can cause obstruction of the ureter. The resulting obstruction causes dilation or stretching of the upper ureter and renal pelvis as well as muscle spasm of the ureter, trying to move the stone. This leads to pain, most commonly felt in the flank, lower abdomen and groin. Renal colic can be associated with nausea and vomiting. There can be blood in the urine, visible with the naked eye or under the microscope due to damage to the lining of the urinary tract. There are several types of kidney stones based on the type of crystals of which they consist. The majority are calcium oxalate stones, followed by calcium phosphate stones. More rarely, struvite stones are produced by urea-splitting bacteria in people with urinary tract infections, and people with certain metabolic abnormalities may produce uric acid stones or cystine stones.

The diagnosis of a kidney stone can be confirmed by radiological studies or ultrasound examination; urine tests and blood tests are also commonly performed. When a stone causes no symptoms, watchful waiting is a valid option. In other cases, pain control is the first measure, using for example non-steroidal anti-inflammatory drugs or opioids. Using soundwaves, some stones can be shattered into smaller fragments. Sometimes a procedure is required, which can be through a tube into the urethra, bladder and ureter, or a keyhole or open surgical approach from the kidney's side. Sometimes, a tube may be left in the ureter to prevent the recurrence of pain. Preventive measures are often advised such as drinking sufficient amounts of water,

although the effect of many dietary interventions has not been rigorously studied.

2.4 Hypertension

Called high blood pressure, hypertension is a chronic medical condition in which the blood pressure is elevated. It is also referred to as high blood pressure or shortened to HT, HTN or HPN. The word "hypertension", by itself, normally refers to systemic, arterial hypertension.

Hypertension can be classified as either essential (primary) or secondary. Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure. It is common. About 90-95% of hypertension is essential hypertension. Secondary hypertension indicates that the high blood pressure is a result of another condition, such as kidney disease (adrenal adenoma) or tumours.

Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. At severely high pressures, defined as mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated. Beginning at a systolic pressure of 115 mmHg and diastolic pressure (which is minimum pressure in the arteries, which occurs near the beginning of the cardiac cycle when the ventricles are filled with blood) of 75 mmHg, cardiovascular disease (CVD) risk doubles for each increment of 20/10 mmHg.

Several lines of research, conducted over several decades, have suggested that sodium intake is causally related to blood pressure. Animal studies have provided much information on the physiology of this relationship. In human studies, cross-cultural population studies comparing cultures with very low salt intake to those with high intakes, and observational studies, most of which were cross-sectional, have suggested that increased salt consumption is associated with higher levels of blood pressure.

2.4.1 Clinical trials and meta-analyses on the effects of salt reduction on blood pressure

Many randomized clinical trials have examined the effect of dietary salt reduction on blood pressure in hypertensive and nonhypertensive people. Modest reduction in sodium intake by about 1.0 g/day resulted in better control of hypertension in older adults who initially are on blood pressure medication. Although some clinicians have questioned the value of modest blood pressure reductions in hypertensive patients, overviews of observational studies and randomized trials suggest that reducing diastolic blood pressure by an average of 2 mm Hg in the U.S. population would reduce the prevalence of hypertension by 17%, the risk of a heart attack by 5%, and the risk of stroke by 15%.

2.4.2 Variation in response to dietary sodium changes: salt sensitivity

There is considerable literature on variation in response of blood pressure to short-term changes in sodium intake. However, classifying individuals based on their blood pressure response to salt changes, usually from an experimental protocol conducted just once, is extremely problematic. Like most physiological responses, there is a continuous, approximately normal distribution of responses of blood pressure to changes in salt intake. There is also variation in blood pressure from day-to-day, even when there is no change in diet. The classification of individuals as salt-sensitive or salt resistant has thus far not been based on population samples and has not yet been shown to be highly reproducible over time. Additionally, most of the protocols used in "salt sensitivity" studies involved extreme manipulations of sodium intake over a short time span of a few days or up to a week. There is no evidence that these very short-term studies have relevance to blood pressure changes occurring from long-term, gradual, and moderate changes in salt intake. Nonetheless, it is well known that certain subgroups of the population tend to have greater average blood pressure responses to changes in sodium intake. These include people who already have hypertension, older individuals, and African Americans. Environmental influences, in addition to genetic factors, likely contribute to salt sensitivity.

2.4.3 Dietary patterns and blood pressure

A multi-center, randomized feeding study, called the Dietary Approaches to Stop Hypertension trial, demonstrated that a diet emphasizing fruits, vegetables, whole grains, poultry, fish, nuts, and low-fat dairy products substantially lowered blood pressure in hypertensive The National High Blood Pressure Education Program and the National Heart, Lung, and Blood Institute of the NIH recommend consuming no more than 6 grams/day of salt, and the Food and Nutrition Board of the Institute of Medicine recently recommended that adults consume no more than 5.8 grams/day of salt. For more information regarding the U.S. dietary guidelines for salt intake, a statement from the National High Blood Pressure Education Program and a summary of the findings of a National Heart, Lung, and Blood Institute workshop on sodium and blood pressure are available online.

2.4.4 Target organ damage

Chronic hypertension damages the heart, blood vessels, and kidneys, thereby increasing the risk of heart disease and stroke, as well as hypertensive kidney disease. In a number of clinical studies, salt intake has been significantly correlated with left ventricular hypertrophy, an abnormal thickening of the heart muscle, which is associated with increased mortality from cardiovascular diseases. Recent research indicates that high salt intake may contribute to organ damage in ways that are independent of its effects on blood pressure. For example, studies in animals and humans have found increased salt intake to be associated with pathological changes in the structure and function of large elastic arteries that are independent of changes in blood pressure.

2.4.5 Cardiovascular disease

Cardiovascular disease or cardiovascular diseases is the class of diseases that involve the heart or blood vessels. While the term technically refers to any disease that affects the cardiovascular, it is usually used to refer to those related to atherosclerosis. These conditions have similar causes, mechanisms, and treatments. In practice, cardiovascular disease is treated by cardiologists, thoracic surgeons, vascular surgeons, neurologists, and interventional radiologists, depending on the organ system that is being treated. There is considerable overlap in the specialties, and it is common for certain procedures to be performed by different types of specialists in the same hospital. Only a few studies have investigated the effects of sodium reduction on cardiovascular disease and on mortality, with mixed results. In general, the studies suggest a direct association, particularly the studies that used urinary sodium as a measure of sodium intake. The process of atherosclerosis evolves over decades, and begins as early as childhood. The Pathobiological Determinants of Atherosclerosis in Youth Study demonstrated that intimal lesions appear in all the aortas and more than half of the right coronary arteries of youths aged 7–9 years.

2.5 Sources

Most of the sodium and chloride in the diet comes from salt. It has been estimated that 75% of the salt intake in the U.S. is derived from salt added during food processing or manufacturing, rather than from salt added at the table or during cooking. The lowest salt intakes are associated with diets that emphasize unprocessed foods, especially fruits, vegetables, and legumes. Recent surveys have found that the average dietary salt intake in the U.S. is 7.8-11.8 g/day for adult men and 5.8-7.8 g/day for adult women. These figures may be underestimations since they did not include salt added to food at the Table 2.

Table 2 lists the sodium content of some foods that are high in salt and some foods that are relatively low in salt. Since the majority of sodium and chloride intake comes from salt, dietary salt content can be estimated by multiplying sodium content by 2.5.

2.6 Safety

2.6.1 Toxicity

Excessive intakes of sodium chloride lead to an increase in extracellular fluid volume as water is pulled from cells to maintain normal sodium concentrations. However, as long as water needs can be met, normally functioning kidneys can excrete the excess sodium and restore the system to normal. Ingestion of large amounts of salt may lead to nausea, vomiting, diarrhea, and abdominal cramps. Abnormally high plasma sodium concentrations (hypernatremia) generally develop from excess water loss, frequently accompanied by an impaired thirst mechanism or lack of access to water. Symptoms of hypernatremia in the presence of excess fluid loss may include dizziness or fainting, low blood pressure, and diminished urine production. Severe hypernatremia may result in edema (swelling), hypertension, rapid heart rate, difficulty breathing, convulsions, coma, and death. Hypernatremia is rarely caused by excessive sodium intake (e.g., the ingestion of large amounts of seawater or intravenous infusion of concentrated saline solution). In end-stage renal failure (kidney failure), impaired urinary sodium excretion may lead to fluid retention, resulting in edema, high blood pressure, or congestive heart failure if salt and water intake are not restricted.

2.6.2 Adverse effects

In 2004, the Food and Nutrition Board of the Institute of Medicine established an upper level of sodium intake of 2.3 g/day (5.8 g/day of salt) for adults based on the adverse effects of high sodium intakes on blood pressure, a major risk factor for cardiovascular and kidney diseases. It should be noted that the upper intake level (UL) for sodium may be lower for those who are most sensitive to the blood pressure effects of sodium, including older people, African Americans, and individuals with hypertension, diabetes, or chronic kidney disease. The upper intake level values for sodium and salt in different age groups are listed in the table below (Table 3).Over intake of sodium has a multi adverse effects in human health.

Table 2. Salt in food

High-Salt Foods			
Food	Serving	Sodium (mg)	Salt (mg)
Bread, whole-wheat	2 slices	264	660
Bread, white	2 slices	340	850
Cereal, corn flakes	1 cup	266	665
Cereal, bran flakes	1 cup	293	733
Dill pickle	1 spear	300	800
Hot dog (beef)	1	510	1,300
Tomato juice, canned (salt added)	1 cup (8 fl. ounces)	650	1,600
Fish sandwich w/ tartar sauce & cheese	1 sandwich	940	2,400
Corned beef hash	1 cup	1,000	2,500
Ham	3 ounces	1,000	2,500
Pretzels, salted	2 ounces (10 pretzels)	1,000	2,500
Potato chips, salted	8 ounces (1 bag)	1,200	3,000
Macaroni and cheese, canned	1 cup	1,300	3,300
Canned, chicken noodle soup	1 cup	1,400	3,400

Low-Salt Foods			
Food	Serving	Sodium (mg)	Salt (mg)
Olive oil	1 tablespoon	0	0
Orange juice (frozen)	1 cup (8 fl. ounces)	0	0
Popcorn, air-popped (unsalted)	1 cup	1	3
Almonds (unsalted)	1 cup	1	3
Pear, raw	1 medium	2	5
Mango	1 fruit	4	10
Tomato	1 medium	6	15
Fruit cocktail, canned	1 cup	9	23
Brown rice	1 cup, cooked	10	25
Potato chips, unsalted	8 ounces (1 bag)	18	45
Tomato juice, canned (no salt added)	1 cup (8 fl. ounces)	24	60
Carrot	1 medium	42	105

Table 3. Tolerable upper intake level (UL) for Sodium and Sodium Chloride (Salt)

Age Group	UL for Sodium (g/day)	UL for Salt (g/day)
Infants 0-12 months	Not Determined*	Not Determined*
Children 1-3 years	1.5	3.8
Children 4-8 years	1.9	4.8
Children 9-13 years	2.2	5.5
Adolescents 14-18 years	2.3	5.8
Adults 19 years and older	2.3	5.8

*Not determined. Intake should be from food or formula only.

2.6.3 Drug Interactions

The following drugs may increase the risk of hyponatremia (abnormally low blood sodium concentration) (Table 4):

Table 4. Families of medications associated with hyponatremia

Families of Medications Associated with Hyponatremia	
Medication Family	Examples
Diuretics	Hydrochlorothiazide, Furosemide (Lasix)
Non-steroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen (Advil, Motrin), Naproxen sodium (Aleve)
Opiate derivatives	Codeine, Morphine
Phenothiazines	Prochlorperazine (Compazine), Promethazine (Phenergan)
Serotonin-reuptake inhibitors (SSRIs)	Fluoxetine (Prozac), Paroxetine (Paxil)
Tricyclic antidepressants	Amitriptyline (Elavil), Imipramine (Tofranil)
Individual Medications Associated with Hyponatremia	
Carbamazepine (Tegretol)	
Chlorpropamide (Diabinese)	
Clofibrate (Atromid-S)	
Cyclophosphamide (Cytoxan)	
Desmopressin (DDAVP; nasal or oral)	
Oxytocin (Pitocin)	
Vincristine (Oncovin)	

2.6.4 Linus Pauling Institute Recommendation

There is strong and consistent evidence that diets relatively low in salt (5.8 g/day or less) and high in potassium (at least 4.7 g/day) are associated with decreased risk of high blood pressure and the associated risks of cardiovascular and kidney diseases. Moreover, a diet emphasizing fruits, vegetables, whole grains, nuts, and low-fat dairy products substantially lowered blood pressure, an effect that was enhanced by reducing salt intake to 5.8 g/day or less. A lower salt intake of 3.8 g/day should be the aim.

2.6.5 Adults over the age of 50

Diets low in salt (3.8 g/day or less) and rich in potassium (at least 4.7 g/day) are likely to be of particular benefit for older adults, who are at increased risk of high blood pressure along with its associated risks of cardiovascular and kidney diseases. Since sensitivity to the blood pressure-raising effects of salt increases with age, diets that are low in salt and high in potassium may especially benefit older adults.

2.7 Sodium retention effectives

Sodium retention and ascites are serious clinical problems in cirrhosis. Urodilatin (URO) is a peptide with paracrine effects in decreasing sodium reabsorption in the distal nephron. The short-term low-dose URO infusion increased the sodium excretion of the patients. The increase was small but systematic and potentially clinically important for such patients. The small response contrasts the preserved responsiveness of the URO receptors. The markedly activated systemic pressor hormones in cirrhosis evidently antagonized the local tubular effects of URO (Carstens et al. 2007).

Renal sodium retention in experimental liver cirrhosis originates from the distal nephron sensitive to aldosterone. Bile duct ligation in mice induces cirrhosis and leads to the induction of sodium- and potassium-dependent adenosine triphosphatase in cortical collecting ducts, to renal sodium retention and to the formation of ascites. Sodium retention, ascites formation and induction of sodium- and potassium-dependent adenosine triphosphatase are independent of the activation of mineralocorticoid receptors by either aldosterone or glucocorticoids (Ackermann et al. 2007).

The pathophysiology of sodium and water retention in heart failure is characterized by a complex interplay of hemodynamic and neurohumoral factors. Relative arterial underfilling is an important signal that triggers heart failure-related sodium and water retention. The response to perceived arterial underfilling is modulated by the

level of neurohormonal activation, the degree of renal vasoconstriction, and the extent to which renal perfusion pressure is reduced. Sodium retention can also be exceeded by water retention, with the result being dilutional hyponatremia. Sodium and water retention in heart failure also function to dampen the natriuretic response to diuretic therapy. The attenuated response to diuretics in heart failure is both disease-specific and separately influenced by the rate and extent of diuretic absorption, the rapidity of diuretic tubular delivery, and diuretic-related hypertrophic structural changes that surface in the distal tubule (Sica 2006).

Body fluid volume regulation by the kidney relies upon the complex interaction of numerous factors. However, in edematous disorders, extrarenal factors can override the 'innate wisdom' of the kidney. For example, in patients with cardiac failure or liver disease and in pregnant women, the normal kidney continues to retain sodium and water despite expanded blood, plasma and extracellular fluid volumes. Such fluid retention can ultimately lead to pulmonary congestion, ascites or peripheral edema. Understanding the kidney's modulation of total body sodium and water in these patients has been perplexing. Cardiac output cannot provide the sole afferent signal for the kidney to regulate sodium and water balance, as the normal kidney can retain excessive amounts of sodium and water when cardiac output is low (e.g. in low output cardiac failure) or high (e.g. cirrhosis or pregnancy). Therefore the integrity of the arterial circulation, which can be impaired either by a low cardiac output or arterial vasodilation, is an important factor in body fluid composition and volume regulation in health and disease (Bekheirnia and Schrier 2006).

Nephropathy is a major contributor to overall morbidity and mortality in diabetic patients. Early renal changes during diabetes include Na retention and renal hypertrophy (DiPetrillo et al. 2003).

A commonly accepted hypothesis is that a chronically high-sodium diet expands extracellular volume and finally reaches a steady state where sodium intake and output are balanced whereas extracellular volume is expanded. However, in a recent study where the main purpose was to investigate the role of natriuretic peptides under day-to-day sodium intake conditions (Heer et al. 2000).

Sodium retention is the most common renal abnormality of cirrhosis and eventually leads to the formation of ascites. The arterial vasodilatation, mainly splanchnic, that occurs during liver cirrhosis is a major factor in the pathogenesis of renal sodium and water retention. The arterial vasodilatation and the subsequent hypotension stimulate a baroreceptor-mediated neurohormonal vasoconstrictor and antinatriuretic response in an attempt to compensate the relative underfilling of the circulation. The cause of the arterial vasodilatation is thought to be a circulating factor and several recent studies have implicated an excessive vascular production of nitric oxide (NO). In animal models of cirrhosis administration of NO antagonists corrects the hyperdynamic circulation and improves renal sodium excretion. The treatment of sodium retention is often difficult in liver cirrhosis and it is possible that the identification of a vasodilator substance which can be inhibited could provide a new tool in the therapeutic approach of sodium and water retention in cirrhosis (Martin 1997).

Renal sodium and water retention and ascites associated with cirrhosis develop in the setting of severe sinusoidal portal hypertension, hyperdynamic circulation (characterized by arterial hypotension, hypervolaemia, high cardiac output and low peripheral vascular resistance), homeostatic activation of the renin-angiotensin-aldosterone system, sympathetic nervous system and antidiuretic hormone production (i.e. mechanisms designed to maintain arterial pressure within normal limits) and marked increase in hepatic and splanchnic lymph production that overcomes the transport capacity of the lymphatic vessels to the general circulation, leading to leakage of fluid within the peritoneal cavity. Splanchnic arteriolar vasodilation and the increased splanchnic blood flow that characterize portal hypertensive states could be a major factor in the pathogenesis of cirrhotic ascites because it may account for the hyperdynamic circulation, the activation of endogenous neurohormonal systems that cause sodium and water retention and, also, by altering of splanchnic capillary haemodynamics and permeability, the excessive production of lymph in this vascular territory (Arroyo and Gines 1993).

Renal sodium and water retention and plasma volume expansion have been shown to precede ascites formation in experimental cirrhosis. The classical "underfilling" theory, in which ascites formation causes hypovolemia and initiates secondary renal sodium and water retention, thus seems unlikely. While the occurrence of primary renal sodium and water retention and plasma volume expansion prior to ascites formation favors the "overflow" hypothesis, the stimulation of the renin-angiotensin-aldosterone system, vasopressin release and sympathetic nervous system associated with cirrhosis is not consonant with primary volume expansion. In this present article, the "Peripheral Arterial Vasodilation Hypothesis" is proposed as the initiator of sodium and water retention in cirrhosis. Peripheral arterial vasodilation is one of the earliest observations in the cirrhotic patient and experimental

animals with cirrhosis. Arterial vasodilators and arteriovenous fistula are other examples in which renal sodium and water retention occur secondary to a decreased filling of the arterial vascular tree. An increase in cardiac output and hormonal stimulation are common features of cirrhosis, arteriovenous fistula and drug-induced peripheral arterial vasodilation. However, a predilection for the retained sodium and water to transudate into the abdominal cavity occurs with cirrhosis because of the presence of portal hypertension. The Peripheral Arterial Vasodilation Hypothesis also explains the continuum from compensated to decompensated cirrhosis to the hepatorenal syndrome (Schrier et al. 1988).

3. Discussion

Sodium and chloride concentrations and export increased from 1986 to 2005 in a rural stream in southeastern New York. Concentrations increased 1.5 mg/l/year (chloride) and 0.9 mg/l/year (sodium), and export increased 33,000 kg/year (chloride) and 20,000 kg/year (sodium) during this period. It estimates that salt used for deicing accounted for 91% of the sodium chloride input to the watershed, while sewage and water softeners accounted for less than 10% of the input. Road salt use in the watershed did not increase during the study, but sodium and chloride from sewage and water softeners is likely to have increased slightly due to a small increase in population. Increased input from sewage and water softeners cannot account for the increase in concentration and export from the watershed. The increase in streamwater concentration and export is likely due to a lag effect of long-term road salt use and subsurface buildup (Kelly et al. 2008).

Salt intake currently in an average person exceeds 10-15 g/day in the world. The key organ responsible for sodium regulation is kidney and renal failure patients present with positive sodium balance. In peritoneal dialysis patients rising hypertension is often connected with volume overload and sodium retention. The reasons for inadequate sodium removal in peritoneal dialysis patients are: too small gradient between standard 134 mmol/l sodium peritoneal dialysis solutions, sodium effect and lack of residual renal function. It has been shown that a degree of sodium removal correlates with survival, sodium management appears to be crucial in the patients. The concept of low sodium solutions has been developed over the years with single-dwell ultra-low solutions and recently with low sodium balance solution given as a continuous treatment in the patients. Preliminary results show that low sodium solutions may be a safe and viable option of treatment of peritoneal dialysis patients with sodium and fluid overload (Lichodziejewska-Niemierko 2008).

Correspondence to:
Yan Yang
Brookdale University Hospital and Medical Center,
Brooklyn, New York 11212, USA,
youngjenny2008@yahoo.com;
1-347-321-7172

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