

# A comprehensive literature review of spermidine

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**Abstract.** This review explores the role of spermidine, a naturally occurring polyamine, in promoting healthy aging and increasing lifespan. Spermidine was initially discovered in human sperm, and it is important in several cellular processes across eukaryotic organisms. We deeply study the historical background of spermidine discovery and its research developments. The paper examines the mechanisms through which spermidine influences lifespan, including its interaction with RNA, stimulation of autophagy, anti-inflammatory effects, and impact on the cell cycle. Each mechanism is discussed with its contribution to cellular health and potential in lifespan extension. Besides, several human diseases that spermidine could reduce the risk of are shown. Moreover, the review highlights food sources of spermidine, especially the Mediterranean diet. Spermidine rich eating pattern is related to improved health outcomes and longevity. Despite the benefits of spermidine, the paper also discusses the potential risks of spermidine intake, indicating that spermidine is related to increased cardiovascular disease risk. In this review, we aim to offer a balanced perspective on how spermidine might help with healthy aging, what we currently know about its effects on the body, and the further research needed to understand what spermidine means for human health.

**Keywords:** Spermidine, polyamine, RNA

## 1. Introduction

Spermidine, a natural polyamine first found in human sperm, plays an important role in the life of eukaryotic organisms. Spermidine has a precursor called putrescine. Spermidine is formed by spermidine synthesis, which is two putrescines being combined. As aliphatic hydrocarbons with amino groups at both ends, polyamines like spermidine are fundamental to nearly all living entities [1]. It increases lifespan and health span, and it could be found in our daily diet.

In 1678, Antonie van Leeuwenhoek, the father of microbiology, discovered crystalline substances in human semen. These crystals, later named “spermine,” were found in semen which had been standing for several days rather than in fresh samples. In 1791, Vauquelin identified these crystals as phosphate derivatives. In 1878, Schreiner classified this compound as an organic base. The name “spermine” was officially introduced by Ladenburg and Abel in 1888. As time passed, the medical potential of spermine was recognized. In 1898, von Poehl confirmed spermine’s therapeutic use for various illnesses. The structure of these polyamines, including both spermidine and spermine, was finally deciphered in 1924 by Rosenheim, which concluded the initial chapter of polyamine research [2].

Today, people are still working on exploring spermidine. Knowledge about the lifespan effects of spermidine continue to be studied, expanding the areas of clinical application.

## 2. Reasons Why Spermidine Increases Lifespan

There are four main reasons why spermidine increases lifespan, which are spermidine interacting with RNA, spermidine stimulating autophagy, spermidine fighting against inflammation, and spermidine affecting cell cycle.

### 2.1. RNA

Spermidines are critical for the regular growth and differentiation of cells in prokaryotes and are necessary for eukaryotic life. In eukaryotes, spermidine is important for activating eukaryotic translation initiation factor 5A (eIF5A), a protein which plays a good role in synthesizing eukaryotic proteins. This process depends on post-translational modifications, and the spermidine acts as a substrate for eIF5A's maturation so that it significantly helps with protein synthesis. Under normal physiological pH, polyamines, including spermidine, are positively charged. This allows them to form weak bonds with intracellular molecules that are negatively charged such as nucleic acids, phospholipids, and ATP. Polyamines, including spermidine, most frequent bind with RNA, which affects the structure of mRNA and therefore regulates protein translation. Such kind of interactions are important for a large number of cellular processes such as proliferation, biofilm formation, activity enhancement, and detoxification. Therefore, it is significant to underline that spermidine and related polyamines are important in maintaining the normal functions of organisms [1].

### 2.2. Autophagy

Autophagy could be seen as a cleanup crew inside human cell. It is a process that helps get rid of damaged or unneeded parts of the cell by breaking them down and recycling them. This process happens in different ways including microautophagy, macroautophagy, and chaperone-mediated autophagy. Macroautophagy is the most common form: the cell's waste is packaged into a structure called an autophagosome, and then fuses with a lysosome or vacuole to break down the contents.

Autophagy keeps cells healthy, but it can increase or decrease based on different factors like aging, stress, or inflammation. For example, as human age, more damaged parts accumulate in cells, and the cells become less efficient at cleaning them up. Autophagy helps fight against aging by removing these damaged parts, therefore autophagy is linked to longer life span and health span.

Spermidine is good at stimulating autophagy in various organisms and cells, from yeast and flies to mice and human cells. There are several ways for it to accomplish it. First, it changes the levels of certain genes (Atg genes) that are involved in autophagy. When these genes are more active, autophagy increases and helps to extend the lifespan. Second, spermidine helps produce more specific molecule (TFEB) that is involved in controlling autophagy. Third, spermidine works by preventing the addition of acetyl groups to proteins involved in autophagy. Spermidine does this by reducing the activity of certain enzymes and the availability of acetyl-CoA, a molecule involved in adding acetyl groups [3].

### 2.3. Anti-inflammatory

Spermidine can increase lifespan because of its anti-inflammatory properties. Inflammation is like human body's alarm system: it fights against infections, but it can also become harmful if the alarm is always on, which leads to "inflammatory aging". This is a major factor in growing older and developing age-related diseases like heart and kidney disease. At this time, spermidine steps in to help calm this inflammation down. There are several ways for spermidine to reduce the body's inflammatory responses. First, spermidine decreases the levels of certain signals (such as TNF- $\alpha$ ) that can cause inflammation, which helps to prevent health issues especially in the heart. It can also stop the accumulation of harmful reactive oxygen species and prevents immune cells from moving to inflammation sites, and therefore together reduce the body's overall inflammatory reaction [3].

Furthermore, spermidine can help convert certain immune cells (macrophages) to a type that does not promote inflammation (M2 macrophages). The M2 macrophages help to control the inflammation. Spermidine accomplishes this by increasing the levels of genes and enzymes that promote this peaceful state. It is especially effective to convert these macrophages during the early life of the macrophages,

which makes them to be anti-inflammatory at the very beginning. In general, all these actions of spermidine work together to reduce chronic inflammation, which helps delay aging and increase lifespan, making spermidine good at promoting a longer, healthier life [4].

#### *2.4. Cell Cycle*

Spermidine could increase lifespan by positively affecting the cell cycle. The cell cycle is a set of checkpoints and stages for a cell to go through so that the cells could grow and divide. Spermidine helps cells go through these checkpoints smoothly, ensuring their healthy growth and division, which leads to healthy human tissues and organs. Studies show that the absence of spermidine can stop cell growth at G1 phase by influencing cell cycle regulators' expression, which indicates the importance of spermidine [3].

There are several methods for spermidine to affect cell cycle. First, spermidine helps promote cells to replicate their DNA and move through the cell cycle, which creates new healthy cells. This is like giving the cells a gentle nudge to keep moving and not get stuck. Additionally, spermidine helps in cell differentiation, promoting cells to become the specific types they need to be, which is important for repairing and maintaining human bodies. Cell differentiation is a process when cells from the same source finally produce cell groups different in morphological structures and functions. Studies shows that spermidine can enhance differentiation in differentiated chondrocytes and in adult stem cells [3].

Moreover, spermidine regulates how cells die. Spermidine can slow down the aging process by avoiding apoptosis. Cell necrosis is the cell death under the induction of extreme serious pathological factors. Studies show that the increase levels of spermidine can suppress cell necrosis, increase the lifespan and improve health in aging yeast [3].

### **3. Human Diseases in which Spermidine Reduces the Risk**

There are five types of human diseases that spermidine can reduce the risk of, and they are all age-related diseases. The first type of disease is metabolic diseases, and the examples are type 2 diabetes mellitus, obesity, and metabolic syndrome. The second type of diseases is musculoskeletal diseases, and the example are Osteoporosis, Sarcopenia, and Osteoarthritis. The third type of disease is immune diseases, and the examples are influenza, cytomegalovirus infection, colitis, and inflammatory bowel disease. The fourth type of disease is cardiovascular disease, and the examples are coronary artery disease, heart failure, and essential hypertension. The fifth type of disease is neurodegenerative diseases, and the examples are Parkinson's disease and Alzheimer's disease [3].

### **4. Foods Rich in Spermidine**

Since spermidine is beneficial for human life span and health span, it is necessary to know what foods are rich in spermidine and spermidine's precursor, putrescine. Fruits and cheese have the highest amount of putrescine, and vegetables and meat products are rich in spermidine.

Products resulting from fermentation processes that involve polyamine-generating bacteria and fungi are rich in spermidine. The content of polyamines in cheese changes between studies. In studied Swedish dairy products, matured cheese has the highest polyamine contents with values of 52.3 and 1.2mg/kg for putrescine and spermidine. Besides, low fat milk has higher putrescine and spermidine, 1.2 and 1.0 mg/kg, than the other types of milk [5].

Spermidine also presents in all unprocessed plant-derived foods, such as fresh green pepper, broccoli, and soybean. The food with the highest contents of spermidine are cereals, legumes and soy derivatives [6].

It is reasonable to indicate that much of the Mediterranean diet contains spermidine rich foods because Mediterranean diet is a plant-based eating plan. The traditional Mediterranean diet is known for its high consumption of plant-based foods, including fruits, vegetables, breads (primarily minimally refined), cereals, potatoes, beans, nuts, and seeds. It emphasizes minimally processed foods that are fresh, seasonal, and locally sourced. Fish and poultry are eaten in low to moderate quantities, while red meat is consumed sparingly [7]. Spermidine increase human life span explains why Mediterranean

dietary pattern raises life expectancy, decreases the risk of chronic disease, and improves human life qualities and well-being. According to studies, the Mediterranean diet is considered the gold standard of preventive medicine, likely because of its harmonious blend of numerous components with antioxidant and anti-inflammatory qualities, which overwhelm the benefits of any individual nutrient or food item [8].

If people struggle to get enough spermidine in their diet, they can also get it as a spermidine supplement.

In summary, adopting a diet rich in spermidine to increase spermidine levels through human body presents a hopeful approach for encouraging healthy aging.

## 5. Risk of Spermidine Intake

The intake of spermidine has been linked to potential health risks, especially concerning cardiovascular health according to studies. One thing that needs to be noticed is that the studies' findings are not yet widely understood or confirmed by large community-based studies. Studies have indicated that higher levels of spermidine in the blood may be related to an increased risk of stroke. To be more specific, individuals with raised serum spermidine levels, especially those with levels at or above 205.9 nmol/L, have been found to have a significantly higher risk of having a stroke compared to those with lower levels. This relationship has been found consistently among several studies, which suggests a strong connection between high spermidine levels and stroke risk. Furthermore, the use of statistical models has confirmed that including spermidine levels in risk assessments can improve the accuracy of stroke predictions [9]. Although spermidine is naturally present in the human body and certain foods, these findings highlight the fact that it is important to know the potential risks associated with spermidine intake, especially for those individuals who have high risk of cardiovascular issues. Therefore, it is necessary to consider carefully and make further research before the spermidine consumption to avoid any potential health risks.

## 6. Conclusion

In conclusion, spermidine, a polyamine discovered in human sperm, has been significant to reach healthy aging and increased lifespan. In this review, we have explored spermidine's several roles in cellular functions, including its interaction with RNA, stimulation of autophagy, anti-inflammatory properties, and influence on the cell cycle. These interactions promote spermidine's ability of prolonging life by maintaining cellular health, preventing premature aging, and fighting against various age-related diseases. We have also discussed how spermidine-rich diets, particularly the Mediterranean diet, can be a natural source of spermidine, which helps preventing chronic illnesses and aging. However, it is also important to balance the benefits with potential risks. It is necessary to know that high spermidine levels have been associated with increased cardiovascular risks like stroke. Therefore, while spermidine could be seen as a helpful supplement to increase life span, further research and a fully understanding are necessary to reduce any potential risks. As we continue to explore spermidine, it is clear that spermidine plays a significant role in the future of health and aging.

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