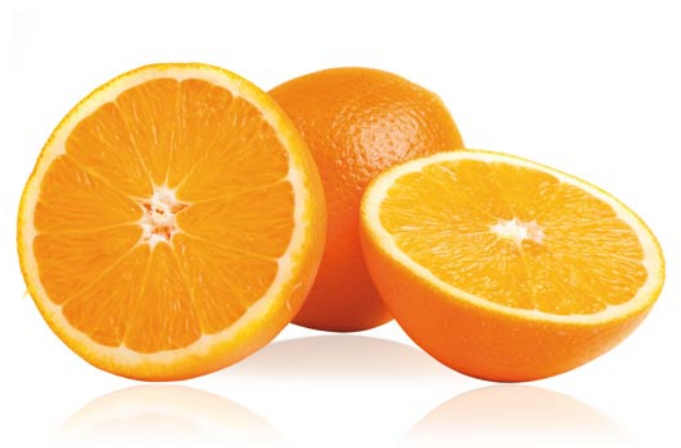
Ascorbic acid – Vitamin C

Healthy, powerful and interfering



Ascorbic acid and its interference with urinalysis results of urine test strips

Albert Szent-Gyorgyi, 1937, Nobel Prize in Medicine: "The only trouble was that scurvy is not a first symptom of a lack but a final collapse, a premortal syndrome and there is a very wide gap between scurvy and full health."

Since the discovery of vitamin C more than 70 years ago scientists have been debating its general impact on human health und its dietary requirement. The possible prophylactic and therapeutic potential in chronic diseases results in sustained and even public interest. Ingesting huge amounts of vitamin C is now common and this means that large quantities are excreted in the urine. Does vitamin C affect urinalysis results?

Ascorbic acid – definition, sources, functions, and consequences

The importance of vitamin C was first discovered in 1747. During the 16th century sea voyagers and sailors died from a disease called scurvy. The British naval physician James Lind found that men suffering from scurvy were cured when given citrus fruits. He published his findings in the "Treatise of the Scurvy" in 1753 developing a hypothesis based on the observed results.[1] He was the first to appreciate the importance of what would be later called vitamin C.

Ascorbic acid ($C_6H_8O_6$) or vitamin C is a six-carbon compound structurally related to glucose. It consists of two inter-convertible compounds, i.e., L-ascorbic

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acid, a reducing agent and L-dehydroascorbic acid, the oxidized derivative. The chemical name is 2-oxo-L-threo-hexono-1,4-lactone-2,3-enediol.[2]

Water soluble vitamin C was first isolated from natural sources and structurally characterized by Szent-Gyorgyi, Waugh and King and first synthesized by Haworth and Hirst in the early 1930s.[3-5] It was first acknowledged in 1937 by the Nobel Prize in Medicine for Szent-Gyorgyi.

Natural sources are fresh fruits and vegetables (e.g., orange, lemons, grapefruit, watermelon, papaya, strawberries, green leafy vegetables, tomatoes, broccoli, etc.). Synthetic ascorbic acid can be obtained in a plethora of supplements being chemically identical to the natural form. There are no known differences in biological activities and bioavailability between the synthetic and the natural variant.[6]

Most plants and animals synthesize ascorbic acid from glucose. Humans and several other primates (e.g., monkeys, guinea pigs, rats) have lost the ability to synthesize vitamin C endogenously as a result of mutations that inactivate the gene, which encodes gulonolactone oxidase (GULO). This enzyme is required for the biosynthesis of vitamin C via the glucoronic acid pathway.[7,8]

Acute lack of ascorbic acid causes scurvy, accompanied by fragile blood vessels, connective tissue damage, fatigue and finally death.

Ascorbic acid is an essential nutrient required for many metabolic functions in humans. It is a cofactor for several enzymes involved in the biosynthesis of collagen and L-carnitine. In concrete terms: vitamin C is required for maintaining normal connective tissue, wound healing and bone remodeling.[9] Furthermore, it acts as a cofactor for several other metabolic reactions, e.g., synthesis of epinephrine from tyrosine and the synthesis of bile acid. Vitamin C involvement is further suspected in thyroxine synthesis, amino acid metabolism, absorption of iron, and adrenal steroidogenesis.[10] As a potent reducing agent ascorbic acid is capable of quenching potentially harmful, free radicals produced by physiological metabolic respiration processes of the body[11], playing an important role in the antioxidant defense system, immune competence, and in strengthening resistance to infection.[12,13] Additionally, vitamin C prevents DNA mutations and might be important in treating certain cancers and chronic diseases.[4-18]

Catabolism of ascorbic acid

Ascorbic acid can be absorbed by active transport in the intestine.[19] Up to 100 mg/day 80-90% can be absorbed. Higher levels reduce the efficiency of absorption.[6] The human body is not able to store vitamin C. The average body tissue of an adult stores 1.2-2.0 g presumably maintained by taking 60-75 mg per day.[20-24] The total body pool of ascorbic acid is saturated by taking approximately 140 mg per day.[25] The average half life of vitamin C amounts to 10-20 days[26], being inversely proportional to the dosage.[24]

Metabolites of vitamin C in the human body are dehydroascorbic acid, 2,3-diketogulonic acid and oxalic acid. They are eliminated via the urine. Urinary excretion starts with plasma ascorbate concentrations of about 1.2-1.8 mg/dL.[27]. They are considered to be the renal threshold. Threshold urinary excretion of ascorbic acid was reported at already 60 mg doses per day.[20,21,24] Ingestion of higher doses of vitamin C results in increased and unchanged excretion without re-absorption by the kidneys.[20-24]

Daily requirements of ascorbic acid

The Recommended Daily Allowance (RDA) of ascorbic acid for humans set by the US Food and Nutrition Board was increased in 2,000 from 60 to 90 mg per day for an adult male.[28] Ingestion of 60 mg/day would prevent the development of scurvy for 30-45 days with a diet lacking vitamin C.[20-23]

But, the recommended intakes vary significantly from 40 mg per day (Dietary Reference Values for Food Energy and Nutrients for the United Kingdom) [29] up to 6,000-12,000 mg per day (Colorado Integrative Medical Centre, Thomas E. Levy)[30]. Linus Pauling's personal use accounted for 6,000-18,000 mg per day.[31] He was the Nobel Prize Winner in Chemistry in 1954 for his "research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances", becoming a proponent of the consumption of vitamin C and other nutrients in high amounts.

Increasing intake of vitamin C and its consequences for urinary excretion

A better understanding of the mechanisms of action of vitamin C, its importance for many physiological processes in the human body, as well as especially its involvement in cancer and heart disease have led to a striking growth not only in academic but also in ordinary interest. Would it be possible for an adequate vitamin C supply to have the potential to benefit public health and to reduce economic and medical costs?

The public interest in healthcare issues, alternative treatment options, such as vitamin supplements and therapies has increased during the last decades. Nowadays a kind of self medication with vitamin C seems to be normal.[32] At present ascorbic acid is the most frequently used vitamin supplement in the world.[6] In 1995 the worldwide annual demand for ascorbic acid was evaluated at 60,000 tons increasing by 50% since 1980.[33] The pharmaceutical industry uses one third of the total produced for vitamin preparations. The food industry makes use of the other two thirds as an additive. Ascorbic acid can be found in nearly all types of packaged food products as a preservative or antioxidant.[34] It can be found on packaging of food as E300, E301, E302, E303, E304. Therefore the ingestion of vitamin C in high doses in food, in tablets as vitamin preparations or food additives, or in fruit juices is very popular. High concentrations of ascorbic acids in urine samples of a normal population are a direct consequence.

An examination of over 4,000 routine urinalysis specimens provided positive results for ascorbic acid in 22.8%.[35] The concentration averaged 370 mg/L with a range of 70-3,400 mg/L. It was shown that an intake of 250 mg/day could produce a mean ascorbic acid level of 310 mg/L, an ingestion of 1,500 mg/day produced a level of 630 mg/L urine.[35]

Significant ascorbic acid levels in urine appear to be common.[36] Laboratories testing urine samples regularly found high amounts of ascorbic acid (≥400 mg/L) [34] in a considerable proportion of a routinely tested population (22.8%).[35] What is the impact of vitamin C on urinalysis results of test strips since high concentrations in urine are so commonplace and frequent?

The potential influence of ascorbic acid on urinalysis results of urine test strips

Most commercially available dipsticks hinge on the peroxidase redox indicator test principle. O-tolidin acting as an indicator is impregnated into filter paper and mounted on a plastic support handle. Dipping the test strip into urine containing hemoglobin, glucose, or other substances to be detected, a change of color occurs. The color change can be evaluated with a reflectometer (urinalysis analyzer) or visually by comparison with an appropriate color chart. High concentrations of ascorbic acid in urine as a test medium can provide false negative results in detecting, e.g., hemoglobin, glucose or others.

Ascorbic acid has the ability to reduce oxidized indicator substances in urine test strips. Therefore, in the case of enzymic dipstick tests, based on the peroxidase redox indicator test principle, it is possible that less color will be produced. Ascorbic acid can interfere with the results in different ways:[37]

- Interference with the oxidase reaction
- Competition as a substrate for peroxidase
- Decoloration
- Auto-oxidation of ascorbate generating free radicals
- Peroxidase-catalyzed production of radicals with ascorbate

Recent studies identified peroxide depletion as the predominant chemical mechanism of ascorbic acid interference.[38] The understanding of these processes contributed to the development of suitable approaches to eliminate the interference of ascorbic acid and to prevent false negative results of urine test strips. As a result clinical findings of potential importance are identified.

One solution could be the routine determination of the ascorbic acid status of urine specimens in order to appraise and correct results accordingly. Another and superior method is to use a urinalysis test strip that is resistant to ascorbic acid.

Ascorbic acid resistant urine test strips

Ascorbic acid resistant dipsticks have to be protected against influences that adulterate results. In order to diminish the interference, ascorbic acid can be oxidized to dehydroascobate acid, incorporating an oxidant into the test strips. It was shown that mercuric acetate can remove the negative impact of ascorbic acid.[37] Impregnation of mesh layers with iodate removes interference of ascorbic acid.[35]

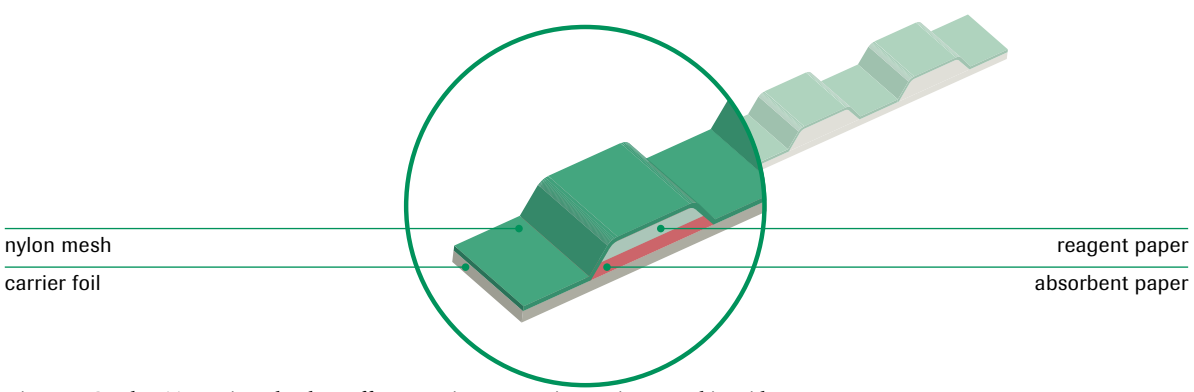

Figure 1: Combur-Test strip technology offers an unique protection against ascorbic acid

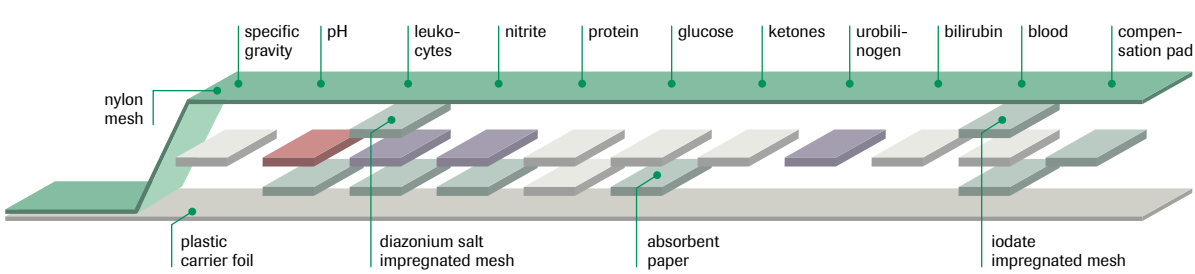

Figure 2: Combur-Test urine test strips from Roche have iodate impregnated mesh layers and are uninfluenced by ascorbic acid

Comparisons between different reagent strips showed the iodate impregnated strip to be most convenient, as it was largely resistant to ascorbic acid interference, when determining both hemoglobin and glucose.[34,35] This iodate impregnated strip is the Combur-Test from Roche (cf. fig. 1). Combur showed the best error tolerance against ascorbic acid in concentrations from 1 to 1,000 mg/L even at higher hemoglobin and glucose levels (cf. fig. 3+4).[34]

Also common today are urine strips which include a pad for the detection of ascorbic acid levels in individual urine samples. But this does not eliminate the problem: adjustment of the result, which may be imprecise, retesting after avoiding vitamin C for 2 to 3 days or a more expensive microscopic examination will be necessary.

Ascorbic acid interference in routine analysis

Hemoglobin
(Target value of 0.075 mg/dL = 25 Ery/µL)

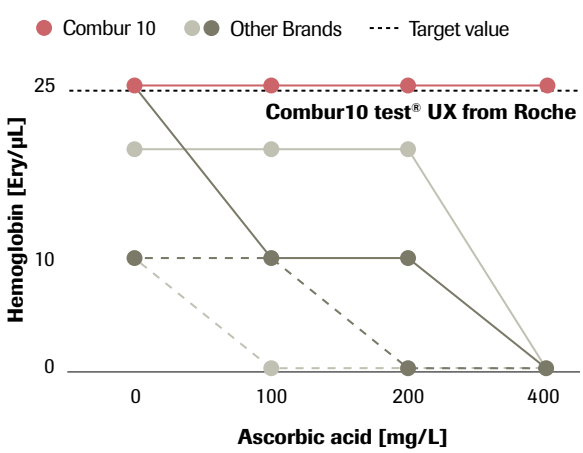

Figure 3: At a hemoglobin concentration of 0.075 mg/dL, Combur-Test strips were the only brand to register a correct analysis with ascorbic acid levels as high as 400 mg/L[1]

Glucose
(Target value of 300 mg/dL)

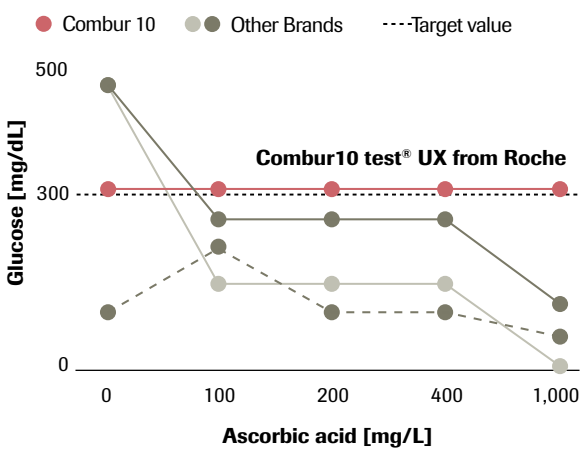

Figure 4: At a glucose concentration of 300 mg/L, Combur-Test strips were the only brand to show consistently accurate results, even at an ascorbic acid level of 1,000 mg/L[1]

Do false negative urinalysis results matter? - Yes they do!

Urine test strips evaluated with a reflectometer or even visually interpreted are commonly used in general practice, in outpatient service or in hospitals. Particularly at times when everyone is streamlining processes and there is a trend towards outsourcing laboratory tests, urine test strips are used to reduce costs. Some authors considered microscopic examination of urine samples to be unnecessary, if the macroscopic urinary inspection and dipstick analysis are normal.[39-42] Although such recommendations have to be evaluated in context, always taking account of all aspects of the patient and his medical history, the danger of false negative results cannot be ignored.

Which patients might be affected negatively from false negative results attributable to interference with ascorbic acid?

Hematuria screening with urine test strips to determine hemoglobin is a well-established method. Urinalysis with urine test strips is used to detect urinary tract disorders of any origin. Microscopic hematuria is defined as the presence of three or more red blood cells per high-powered field in a centrifuged urine specimen in two of three samples.[43-46] There is no correlation between the degree of hematuria and the severity of the underlying condition. Therefore it should be considered a symptom of a serious disease until proved otherwise. Common causes of hematuria are [47]

- Glomerular causes, e.g.:
  familiar (Fabry's disease, Alport's syndrome, Nail-patella syndrome etc.)
  primary glomerulonephritis (Goodpasture's disease, IgA nephropathy etc.)
  secondary glomerulonephritis (Hemolytic-uremic syndrome, vasculitis etc.)
- Renal (nonglomerular) causes, e.g.:
  arteriovenous malformation, malignant hypertension, papillary necrosis etc.
- Urologic causes, e.g.:
  tumors (cancer: kidney, ureteral, bladder, prostate, urethral), calculi, infections etc.
- Other causes, e.g.:
  drugs, trauma, exercise induced etc.

Microscopic hematuria is often an incidental finding and may be associated with urologic malignancy in up to 10 percent of adults.[48,49] Therefore positive dipstick testing, although often intermittent, should not be ignored.

Dipstick results should be compared routinely to phase-contrast microscopy examinations. Also it could be shown, that even routine urine microscopy in the microbiology laboratory sometimes lags behind standards. Reasons could be the lysis of red blood cells during voiding and microscopy, the use of bright-field microscopy, or not being experienced and devised to quantify low-level hematuria.[50] For instance:

- In 35 of 63 patients with asymptomatic dipstick-positive hematuria, microscopic detection was not possible. Two of these 35 patients had bladder cancer[51]
- 4 of 86 patients with dipstick-positive and microscopy-negative hematuria had a urological malignancy, only 15 of these 86 patients showed no abnormality[52]
- 2 of 53 patients with asymptomatic dipstick hematuria had urological malignancies, 2 had stones, 4 had a benign prostatic hyperplasia[51]
- One screening detected poor consensus between dipstick and microscopic laboratory urinalysis[53]
- Another study showed significant urological abnormalities in 8 of 11 patients with positive dipstick and negative microscopy results[54]

One author concluded hematuria proven with dipstick testing as predictive as verification with routine laboratory microscopy.[50] It has to be considered,

- That asymptomatic hematuria, being widespread especially in older age, might be classified as normal
- That asymptomatic hematuria is not associated with an increased risk of urological malignancies measured against the whole population, but doubling the risk, if patients develop renal failure as a consequence
- That the examination of asymptomatic hematuria amongst high risk populations (e.g., older men) results in high incidence of malignancies

Therefore positive findings in urinalysis results of urine test strips should be further evaluated [55] in any case, especially in high risk patients. Also in

young, non-risk patients a screening and, if positive, additional diagnostic measures are necessary. For instance, hematuria can be an absolute contraindication for recipients or donors prior to renal transplantation. Hematuria will make further roentgenologic, cystoscopic, or cytologic investigations indispensable. [56,57]

Positive results for hemoglobin could be an indicator of treatable and appreciable disorders.[54,58,59] Of course, any further diagnostic or therapeutic procedures required are ruled out, if the examination is falsely negative, e.g., as a result of ascorbic acid interference.

One study showed that 109 of 407 ascorbate-positive urine specimens to detect hemoglobin would have been missed due to ascorbic acid influence.[35] Consequences for patients could be devastating. Diseases or alterations identified too late or not identified at all, have possible negative effects not only for the individual person but also for society.

False negative results of urinary glucose testing are likewise not desirable. A diabetic patient being tested for glucose can be badly affected. Intensification of diabetic therapy may be missed due to a negative or only weakly positive result. Wrong therapy management could have potentially dangerous and detrimental consequences.

Urine reagent strips are a useful tool for investigating, diagnosing and screening diseases immediately. Reliable and precise results are important, since adulterated results can lead to false negative results or re-testing of patients.

The influence of ascorbic acid on urine test strip pads for hemoglobin and glucose can be largely excluded using iodate impregnated mesh layers such as applied in the Combur-Test.

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