Serum 3-Nitrotyrosine May Be Elevated With the Exposure to Acute Inflammatory Risk Factors Such As Unhealthy Diet, Pollutant, Drug and Psychosocial Stress

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Serum 3-nitrotyrosine (3NT) is a marker of oxidative and nitrosative stress. Detection of elevated serum 3NT has been considered as the result of exposure to peroxynitrite, a potent oxidant, and to be at risk of developing life-threatening degenerative diseases such as cardiovascular disease, stroke, renal failure and cancer. However, recent literature has reported that 3NT is also a highly sensitive marker in response to a short exposure to many acute risk factors of inflammation such as unhealthy diet, pollutant, toxic substance, drug and even the psychosocial stress. In these cases elevation of 3NT was detected in a few days before any cell damages became apparent. Therefore it should be noted that it is possible to detect elevated 3NT in healthy asymptomatic individuals because of their frequent exposure in their daily living to these acute risk factors, and is not necessary a sign of poor prognosis.

Key words: 3-nitrotyrosine, nitric oxide, superoxide, peroxynitrite, inflammation, oxidative stress, nitrosative stress

Marker of inflammation, oxidative and nitrosative stress

Amino acid tyrosine residue, either free or of a protein, can be nitrated to form 3-nitrotyrosine (3NT). Two molecules, namely nitric oxide (NO) and superoxide (O2−), are required for the nitration reaction [1]. Because the generation of 3NT involves both the reactive oxygen species (ROS) such as superoxide and hydrogen peroxide and the reactive nitrogen species (RNS) in nitric oxide, therefore, 3NT is being considered as a marker of oxidative and nitrosative stress. 3NT is also a marker of inflammation since the production of both ROS and RNS usually takes place at the inflammatory site and is promoted by inflammation.

Presence of peroxynitrite and its clinical impact

There are two major pathways leading to the production of 3-nitrotyrosine (3-NT). One pathway is mediated through the formation of peroxynitrite (ONOO−) and the second pathway is catalyzed by the heme-containing peroxidases, mainly the myeloperoxidase (MPO). The peroxynitrite-dependent pathway appears to be the predominant route in protein nitration in vivo [1]. The detection of 3NT in biological samples is considered in general as the result of exposure to peroxynitrite [2]. Peroxynitrite is known to be a potent oxidant capable of causing cell death and tissue damage as manifested in many human diseases including many neurological disorders, coronary artery disease (CAD), stroke, and many inflammatory diseases. Conceivably detection of serum
3NT has been considered as a sign of poor prognosis.

**Elevation in inflammatory diseases**

As a marker associated with inflammation, especially the chronic inflammation, it is not surprising that elevation of serum 3NT has been detected in various inflammatory diseases [3]. Elevated serum 3NT has been detected in cardiovascular disease (CVD) [4], in chronic renal failure (CRF) [5], and in patients undergoing hemodialysis [6]. Elevation of 3NT has been found to cause DNA damage [7], detected in cancer and to be correlated with the expression of angiogenesis factor and lymph node metastasis [8]. It should be noted that the pathogenesis and progression of all of these inflammatory diseases have been known to be associated with chronic inflammation as a result of long time exposure to persistent risk factors of inflammation such as central obesity, abnormal lipid profile, infection and hyperglycemia mentioned above [9].

**A sensitive marker in response to acute risk factors of inflammation**

However, reports in the recent literature indicate that 3NT may also be a very sensitive marker responding to a short exposure to various acute risk factors of inflammation. Elevated serum 3NT can be detected in a few days following a short exposure to risk factors mentioned above, long before any cell damages become apparent. It is important to realize that the onset of most inflammatory diseases takes at least months, if not years, to take place under the long-time, persistent exposure to risk factors of inflammation [9].

As shown in Table 1 elevated serum 3NT can be detected at the early stage of chronic inflammation in individuals exposed only a few days to acute risk factors of inflammation [10]. Elevated 3NT has been detected in individuals a few days after consuming unhealthy diet such as diet containing elevated cholesterol [11], high-fat or high sugar [12,13].

The highly sensitive 3NT in response to many acute risk factors of inflammation can be further demonstrated by detecting elevated 3NT in individuals taking strenuous exercise [14], smoking [15], or exposed to asbestos [16] and toxic substances such as arsenic [17]. Elevated serum 3NT has also been detectable in elderly [18]. Because it is known that psychosocial stress will induce chronic inflammation [19], therefore, we also anticipate that elevated serum 3NT is detectable in asymptomatic individuals with psychosocial stress. Conceivably it should not be surprising why elevated 3NT has so frequently been detected in apparent healthy individuals. It is almost inevitable for any of us not to be exposed to these acute risk factors of inflammation in our daily living. Therefore it is important to realize that detecting elevated serum 3NT in an individual is not necessarily an indication that the person is associated with severe inflammatory diseases. Detection of elevated 3NT in asymptomatic individuals could most likely the result of a short transient exposure to excess superoxide and nitric oxide produced by acute inflammatory risk factor(s).

**Response to food supplement and medication**

It should be noted that the level of serum 3NT could be subjected to change, mostly a reduction, by the administration of nutritional supplementation such as vitamin C and vitamin E [20, 21], and green tea [22]. It has been reported that medication such as statins can also effectively reduce the level of serum 3NT [4, 23].

**Table 1. Elevation of serum 3NT is detectable in individuals with a short-exposure to many inflammatory risk factors in the diet and in the environment**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comment</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Exhaustive exercise</td>
<td>Such as marathon race</td>
<td>14</td>
</tr>
<tr>
<td>Hyperglycemia diet</td>
<td>Postprandial hyperglycemia</td>
<td>12, 13</td>
</tr>
<tr>
<td>High cholesterol diet</td>
<td>A short term diet</td>
<td>11</td>
</tr>
<tr>
<td>High fat diet</td>
<td>Elevated triglyceride from high fat or hyperglycemic diet</td>
<td>12</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Environmental toxicity</td>
<td>16</td>
</tr>
<tr>
<td>Smoke</td>
<td>Cause airway inflammation</td>
<td>15</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Cause inflammation</td>
<td>17</td>
</tr>
<tr>
<td>Associated with aging</td>
<td>May not be an acute inflammation</td>
<td>18</td>
</tr>
<tr>
<td>Psychosocial stress</td>
<td>Cause inflammation</td>
<td>19</td>
</tr>
</tbody>
</table>
References


血清 3-硝化酪胺酸會因暴露於急性發炎危險因子
如不健康的飲食、污染物、藥物和心理的壓力而升高

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血清的3-硝化酪胺酸(3-硝胺酸)一向被認為是一個氧化損傷的標誌。一般而言，當血液中偵測到3-硝胺酸的升高，這表示身體遭受到氧化壓力的傷害。如果3-硝胺酸繼續升高，則代表有發展成威脅生命的疾病的危險，這些致命疾病包括：心血管疾病、中風、腎臟衰竭及癌症。但最近研究報告指出，當人體只是遭遇短暫、輕微的危險因子，如不健康的飲食、環境污染、毒性物質、藥物、甚至於心理壓力時，3-硝胺酸亦可很快地反應出來，因此可當作一個非常靈敏的檢驗指標，在遭遇這些危險因子幾天之內，細胞並無損傷之前，血清3-硝胺酸就會升高。換言之，若每天生活暴露於這些危險因子之下，人在正常的情況下3-硝胺酸也會升高，這不完全代表遭受氧化損傷的結果。

關鍵詞: 3-硝化酪胺酸、一氧化氮、超氧自由基、過亞硝酸根、發炎、氧化壓力、硝酸化壓力