Method of Defining Equol-Producer Status and Its Frequency among Vegetarians$^{1,2}$

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Abstract

7-Hydroxy-3-(4'-hydroxyphenyl)-chroman (S-equol) is a specific end-metabolite formed in the biotransformation of the dietary soy isoflavones daidzin and daidzein by intestinal bacteria. The frequency of equol production varies among individuals and populations, and it is suggested that the efficacy of soy foods differs depending on the ability of an individual to produce equol. To develop a standardized approach to define equol-producer status that can be universally adopted to differentiate these 2 distinct populations, we measured isoflavones in serum and urine collected from a cohort of 41 healthy adults, comprising 29 vegetarians and 12 nonvegetarians, after consuming 2 × 250 mL/d soy milk on 3 consecutive days. Serum and urinary daidzein and S-equol concentrations were analyzed by MS. Serum S-equol and daidzein concentrations ranged from 10.3–139 nmol/L (2.5–33.6 µg/L) and 16–1401 nmol/L (4.0–356 µg/L), respectively, whereas in urine the corresponding concentrations ranged from 16–12,574 nmol/L (4.0–3043 µg/L) and 539–26,834 nmol/L (137–6816 µg/L), respectively. The log$_{10}$-transformed urinary S-equol:daidzein ratio provided a clearer distinction of equol-producer status than the absolute serum or urinary S-equol concentrations because it is independent of isoflavone intake and minimizes interindividual variation in isoflavone pharmacokinetics or differences in analytical methodologies. A threshold value for the log$_{10}$-transformed urinary S-equol:daidzein ratio of –1.75 provided a demarcation to define equol-producer status. The frequency of equol producers in the vegetarians was 59%, similar to the reported frequency in Japanese adults consuming soy, and much higher than for nonvegetarian adults (25%), suggesting that dietary components other than soy influence S-equol synthesis by intestinal bacteria. J. Nutr. 136: 2188–2193, 2006.

Introduction

7-Hydroxy-3-(4’-hydroxyphenyl)-chroman [(-)S-equol]$^6$ is a nonsteroidal estrogen (1,2) and a key metabolite of daidzin (3,4), one of the predominant isoflavones found in most soy foods (5–7). It is formed in the colon by an initial hydrolysis of the glucoside moiety (8,9) and then by the action of colonic bacteria (4,10) that perform an enantiomeric-specific reaction to produce exclusively the S-equol diastereoisomer (11). This asymmetric synthesis is of physiological relevance because S-equol is a selective estrogen receptor modulator having a high affinity for estrogen receptor-β (ERβ; Ki = 0.73 nmol/L), whereas the other diastereoisomer R-equol has poor affinity for both estrogen receptors ERα and ERβ (11,12). S-Equol also is unique in that it is also a potent antagonist of dihydrotestosterone, a property that suggests a role for equol in androgen-mediated pathologies, such as prostate cancer and skin conditions (13).

Although almost every animal species studied produces equol when fed soy-containing diets (14), humans differ in that only 20–35% of the Western adult population is capable of producing S-equol when fed soy foods or isoflavone supplements (4,10,14–16). A higher frequency of equol producers, ~50–55%, is found in adults living in Asian countries where soy is consumed with regularity (17,18), and the reasons for this are most likely related to differences in the macrocomposition of the diets (14). Several recent studies suggest that those who are equol producers show more favorable responses to soy isolavone-containing diets (14), indicating that the metabolite S-equol has greater biological potency than either daidzein or genistein, the aglycon forms of the 2 principal soy isoflavones.

The equol producer is defined from urinary or serum equol concentrations and determining this requires the consumption of the soy foods or isoflavone supplements containing daidzin or daidzein (4,15,16). Due to the fact that S-equol formation largely occurs in the distal intestine and colon (4), its formation is time dependent and, therefore, a single serving of soy or isoflavones may be insufficient to accurately define an equol producer. Because different arbitrary cutoffs for urinary and serum equol concentrations have been used to differentiate equol producers from nonproducers (14), the amount of isoflavone consumed will greatly influence this assignment. Variations in analytical
measurement of S-equol (14) further compound the problem of using a specific threshold equol concentration that can be applied universally. There is thus a need to adopt a universal approach to defining equol-producer status so that accurate classification can facilitate clinical studies of soy foods where differences in clinical responses to isoflavones seem apparent (14). We propose an approach to resolve this problem, by expressing equol production on the basis of the log_{10}-transformed ratio of S-equol concentration to its precursor daidzein after a soy isoflavone challenge, and have validated this in a cohort of healthy adults.

**Subjects and Methods**

**Human Studies.** Healthy adults (n = 41) aged between 26 and 64 y, 18 females and 23 males, were studied. Subjects with preexisting gastrointestinal or liver disease or who had taken antibiotics in the preceding 3 mo were excluded from study. No dietary restrictions were imposed and subjects continued to consume their usual diets. Each subject was asked about their usual dietary preferences and broadly classified as consuming a mixed diet or vegetarian diet. A subject who normally consumed meat no more than once per week was classified as vegetarian. Each subject was given daily, on 3 consecutive days, 2 glasses (250 mL) of a commercially available soymilk (So Good; Sanitarium Health Foods), 1 in the morning and 1 in the evening. On the morning of day 3, each subject voided their bladder and began collection of a complete pooled 24-h urine sample that was stored at 4°C during the collection period. The 24-h urine volume was recorded and 50 mL of the urine was frozen until required for analysis. On the morning of d 4, a single blood sample (10 mL) was obtained by venepuncture of the antecubital vein. The blood was centrifuged at 1200 × g for 10 min, and the serum was removed and stored at −20°C until analyzed. The samples were obtained by staff of the Pathology Department of the Sydney Adventist Hospital, Sydney, Australia, and informed consent was obtained. The study was performed according to a protocol approved by the Human Investigation Committee of the Sydney Adventist Hospital.

**Analytical Methodology.** S-Equol, daidzein, and genistein concentrations were measured in serum by GC-MS and in urine by HPLC with electrospray ionization (ESI)-MS. These methods have been described in detail elsewhere (19–21) and are outlined below.

**Measurement of S-equol and isoflavone concentrations in serum by GC-MS.** The concentration of S-equol, daidzein, and genistein in serum (0.5 mL) was measured by stable-isotope dilution GC-MS with selected ion monitoring after addition of [2-13C]equol, [2-13C]daidzein, and [2-13C]genistin, the stable-labeled analogs used as internal standards for quantification. Isoflavonoids were extracted on a solid-phase, octadecylsilane-bonded silica cartridge; hydrolyzed enzymatically with a mixed β-glucuronidase-sulfatase preparation (Helix pomatia; Sigma Chemicals); and, after reextraction and purification, the tert-butyldimethylsilyl ether derivatives were prepared. The derivatized samples were analyzed by selected ion monitoring GC-MS as exactly described previously (19–21).

**Measurement of S-equol and isoflavones in urine by ESI-MS.** Urine (50 μL) samples were diluted with 10 mL of 0.05 mol/L sodium acetate buffer (pH 4.5) and hydrolyzed overnight with 0.1 mL of a mixed β-glucuronidase-sulfatase preparation (H. pomatia; Sigma Chemicals). S-Equol and the soy isoflavonoids daidzein and genistein were then extracted by a solid-phase, octadecylsilane-bonded silica cartridge and recovered by elution with methanol (3 mL), which was evaporated under a stream of nitrogen gas. The urine extract was dissolved in 100 μL of the HPLC mobile phase and a 20-μL sample was injected on column. ESI-MS was performed on a Macromass Quattro liquid chromatography-MS. The HPLC effluent to the ESI probe was split 10:1. The desolvation temperature was 300°C and the source temperature was 100°C. The sampling cone was held at 50 volts and the extractor at 2 volts. Data were collected in the negative ion mode, and the [M-H]⁻ ions monitored were mass-to-charge ratio (m/z) 241 (S-equol) and m/z 242 ([2-13C] S-equol), and m/z 255 (daidzein) and m/z 256 ([2-13C]daidzein). The identity of S-equol, daidzein, and genistein was based on the retention time of the eluting peak in the mass chromatogram compared with the mass chromatograms obtained for the added stable-labeled analogs. Quantification of S-equol, daidzein, and genistein was achieved by calculating the area ratio of the isoflavone to its stable-labeled analog and interpolation of this value against calibration curves constructed of known concentrations of pure standards.

**Data Analysis.** Serum and urinary S-equol and daidzein concentrations were expressed as nanomoles/liter and micrograms/liter. These data were grouped according to dietary habit of the subject (vegetarian or nonvegetarian) and in ascending order of concentration, and when analyzed were expressed as mean ± SEM. The ratio of S-equol to daidzein was calculated, transformed, and expressed as log_{10}. Subjects with a log_{10} urinary S-equol:daidzein concentration ratio above −1.75 on this scale were classified as equol producers. To measure the association between S-equol-producer status and dietary habits or gender, the odds ratio, its 95% CI, and a significance level were calculated under a logistic model (22). When this study was planned, we had no information on the order of magnitude of the frequency of S-equol producers we would find and could not specify any difference worth detecting. Accordingly, study power could only be estimated retrospectively.

**Results**

All 41 adults completed the study. Within this cohort, the proportion of vegetarians as determined from a dietary questionnaire was 71% (29 of 41) and those consuming a mixed diet accounted for the remainder (12 of 41, or 29%). The soy protein drink used in the challenge test to define equol-producer status contained 64.6 mg/L total aglycon-equivalent forms of isoflavones, comprising 28.1 mg/L daidzein and its conjugates (7).

S-Equol and daidzein concentrations ranged from 10–139 nmol/L (2.5–33.6 μg/L) and 16–1401 nmol/L (4.0–356 μg/L), respectively, whereas in urine the corresponding concentrations ranged from 16–12,574 nmol/L (4–3043 μg/L) and 539–26,834 nmol/L (137–6816 μg/L), respectively. The absolute serum and urinary S-equol concentrations in the individual subjects after consuming 500 mL of a soy milk drink (250 mL twice daily) for 3 consecutive days are shown (Fig. 1, upper panel). These graphs are expressed in rank order of serum S-equol concentration within the vegetarian and nonvegetarian groups, respectively. A wide variation in serum S-equol concentrations was observed, but within these defined groups the plots showed 2 distinct clusters: a group of subjects that had a very low serum S-equol concentration and a group with a progressively increasing concentration. A distinct separation between these 2 groups was noted at a serum S-equol concentration of 20 nmol/L (5 μg/L), and, using this threshold to differentiate equol producers from nonequol producers, the proportion of equol producers within the entire cohort was 46% (19 of 41). However, only 4 of 12 (33.3%) of the nonvegetarian group were equol producers compared with 15 of 29 (51.7%) of the vegetarians.

Comparable plots of urinary S-equol concentration for the same subjects are shown in Figure 1 (lower panel). Again 2 distinct clusters were observed, with a demarcation at 82 nmol/L (20 μg/L) separating equol producers from nonequol producers. Based on this separation, 25 of 41 (60.9%) of the cohort were defined as equol producers. Of the nonvegetarians, 4 of 12 (33.3%) were equol producers compared with 21 of 29 (72%) of the vegetarians. Although there was a linear relationship between serum and urinary S-equol concentrations (r = 0.69,
P < 0.001), the high degree of scatter (Fig. 2) explains the poor comparison in assigning frequency of equol producers within populations based on the 2 approaches.

Because absolute S-equol concentration will be strongly influenced by the exposure level to soy isoflavones and also by interindividual variations in isoflavone pharmacokinetics, to circumvent these variables the serum and urinary S-equol concentrations were compared with daidzein concentrations and the values expressed as a ratio of S-equol to daidzein consistent with the product-precursor relation.

The log$_{10}$-transformed ratios of S-equol to daidzein concentrations for serum and urine are compared (Fig. 3). Using the log$_{10}$-transformed data, a clear distinction was evident between equol producers and nonequol producers only for the urinary values. A cut-off log at $-1.75$ (absolute ratio $= 0.018$) for urine yielded a clear demarcation of 2 distinct groups, and, based on this threshold value, the overall proportion of equol producers within the entire cohort was 48.8% (20 of 41). Based on the log$_{10}$-transformed data, the proportion of equol producers was 59% (17 of 29) in the vegetarian group and 25% (3 of 12) in the nonvegetarian group. Vegetarians were 4.25 times as likely to be S-equol producers (95% CI: 0.95–19; $P = 0.059$) as nonvegetarians. The log-transformed data for serum yielded a relatively linear curve for both the vegetarians and nonvegetarians, with no clear demarcation separating equol producers from nonequol producers, and this ratio was not useful in assigning equol-producer status.

The frequency of equol producers assigned by the 3 different approaches (serum S-equol concentration, urinary S-equol concentration, and the log$_{10}$-transformed ratio for urinary S-equol to daidzein expressed for the entire cohort; subdivided according to whether they were vegetarian or nonvegetarian subjects) is examined (Table 1). The frequency of equol producers within the vegetarians was consistently higher than the frequency of equol producers in nonvegetarians, irrespective of the approach used to define equol production.

Overall, there was a good agreement in assigning the equol-producing status of individuals among the 3 approaches, with 28 of 41 subjects being assigned the same classification. Where the serum or urinary S-equol concentrations were close to the assigned threshold levels, differences in classification were more apparent. Experimental error influences the classification much more in this region than it does further away from the threshold, and for this reason the log$_{10}$-transformed urinary S-equol:daidzein ratio was adopted as the standard approach to define equol producers.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Urine S-equol concentration (nmol/L)</th>
<th>Serum S-equol concentration (20 μg/L)</th>
<th>Log$_{10}$ urine S-equol:daidzein ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined threshold</td>
<td>82 nmol/L (20 mg/L)</td>
<td>20 nmol/L (5 μg/L)</td>
<td>$-1.75$</td>
</tr>
<tr>
<td>All subjects ($n = 41$)</td>
<td>60.9 (25)</td>
<td>46.3 (19)</td>
<td>48.8 (20)</td>
</tr>
<tr>
<td>Vegetarians ($n = 29$)</td>
<td>72.4 (21)</td>
<td>51.7 (15)</td>
<td>58.7 (17)</td>
</tr>
<tr>
<td>Nonvegetarians ($n = 12$)</td>
<td>33.3 (4)</td>
<td>33.3% (4)</td>
<td>25% (3)</td>
</tr>
</tbody>
</table>

1 Values are % (n).
equol-producer status because this reflects the product-precursor relation and will be independent of the dietary intake of isoflavones. The agreement between the urinary $S$-equol:daidzein ratio and the urinary $S$-equol concentration was consistent, with only 3 differences in classification being observed. Comparing classification with the serum $S$-equol concentration yielded 12 differences among the 41 subjects, indicating serum $S$-equol concentrations are less informative in defining equol-producer status.

In considering gender differences within the total cohort, 15 of 23 (65%) of the males and 5 of 18 (28%) of the females produced $S$-equol. Men were 3.11 times more likely to be $S$-equol producers (95% CI: 0.86–11; $P = 0.084$) than women.

**Discussion**

Interest in the role of $S$-equol, a key metabolite of the soy isoflavones daidzin and daidzein, has grown significantly in recent years following the so-called equol hypothesis, contending a greater efficacy of soy protein or soy food diets in people that have an active bacterial flora capable of converting daidzein into $S$-equol (14). Although the nature of the bacteria responsible for $S$-equol production remains unclear, several studies have isolated bacterial species purported to perform this conversion at least in vitro (23–25) (U.S. Patent 6,716,424). Whether these same bacteria are active in vivo within the lumen of the colon is unknown or whether the specific colonic bacterial species that make $S$-equol are difficult to isolate in vitro is a further possibility for the slow progress in elucidating the mechanism of synthesis of $S$-equol. It is evident that there must be more than 1 bacterial strain involved because $S$-equol synthesis proceeds through the intermediate dihydrodaidzein (14,24–26) and antibiotic administration has been shown to influence differently the excretion of dihydrodaidzein and $S$-equol (27). Equol is particularly interesting in existing in 2 possible diastereoisomers, and our recent studies have conclusively shown that it is $S$-equol (not $R$-equol) that is produced in humans when soy isoflavones are ingested by equol producers (11). This distinction is important because, although both equol enantiomers have been found to be potent antagonists of dihydrotestosterone action (13), only $S$-equol shows significant binding to the estrogen receptor, and this is highly selective toward ERβ (11,12). We are unaware of any other molecule that possesses both antiandrogen action while also being a ligand for the ER, and this uniqueness of $S$-equol, we believe, may explain the apparent greater efficacy of soy isoflavone-containing diets in equol-producing subjects.

The assignment of equol-producer status has been rather arbitrarily determined by a number of different criteria. Threshold concentrations of $S$-equol in urine or serum have been chosen based upon the distinct clustering of subjects into low or negligible levels and those with significantly high levels (4,15,16). Inevitably there will always be a few subjects that may fall into an intermediary position, and whether this can be explained by recent use of antibiotics or other factors that transiently reduce the activity of the $S$-equol-producing bacterial enzymes remains a possibility. Alternatively, some subjects may have the ability to convert daidzein to dihydrodaidzein but not to proceed to $S$-equol; they are considered partial converters.

The threshold values used to define an equol producer have differed among studies, which may be due to analytical differences in measuring $S$-equol. There is consequently a need for a universal and consistent approach to defining equol-producing status. Using an absolute $S$-equol concentration threshold for either urine or serum is problematic because the concentration of $S$-equol in serum or urine is influenced by the mass of daidzein and its conjugates consumed, and by the pharmacokinetic behavior and bioavailability of isoflavones. Although the former can be controlled by a standardized challenge of soy isoflavones, as was advocated by Lampe et al. (15) and executed in this study (total daidzein aglycon equivalents consumed was 14 mg/d for 3 d), the latter is highly variable among individuals (17,19–21,28–31). Although dietary records were not obtained during the soy challenge, it was known from interviews during enrollment that a significant number of the participants in the study were long-term regular users of soy. Challenging these individuals with soy milk for 3 d consequently provides daidzein in addition to that derived from the usual dietary isoflavone intake, and this will consequently influence the absolute serum and urinary $S$-equol concentration measured, as well the timing of blood collection. Furthermore, an individual can only be an equol producer if soy isoflavones are ingested, and, therefore, in clinical studies compliance to isoflavone intake is crucial in defining equol status when adopting threshold values of $S$-equol concentrations.

In searching for a sounder basis for classifying equol-producing status and to overcome the above limitations in using absolute $S$-equol concentration, we examined several different treatments of the data generated from a cohort of healthy free-living subjects that included a high proportion of vegetarians. By first sorting the serum and urinary concentration data for the cohort into numerical order and plotting these data (Fig. 1), the presence of a step or inflection occurs at a dividing line between producers and nonproducers, with the threshold concentrations being, respectively, 20 nmol/L (5 µg/L) for serum and 82 nmol/L (20 µg/L) for urine. This has been a consistent observation in previous studies (4,15,16). Urine and serum $S$-equol levels were positively correlated ($r = 0.69, n = 41, P < 0.001$). However, the correlation is not sufficiently high (Fig. 2) to give a good predictive regression relation; only 48% of the variance is explained by the correlation ($r^2 = 0.48$). We therefore expect that there will not be complete agreement between equol status classification based on absolute serum and urine concentrations as was evident from this study (Table 1). Where a subject is an obvious equol producer, the $S$-equol concentration in both urine and serum will be a long way from the threshold between equol producers and nonequol producers and quite large experimental variance will not affect the classification. It is in the region close to the threshold value that experimental variation will be significant and defining equol-producing status may be more difficult.

$S$-Equol is the specific metabolite and end product of daidzin or daidzein biotransformation by intestinal bacteria. Therefore, expressing this product-precursor relation as the ratio of $S$-equol to daidzein compensates for variability in isoflavone intake or systematic errors in methodologies for isoflavone measurement, and provides a more reliable indicator of the extent of conversion of daidzein into $S$-equol. Log-transforming these data permits a better definition of this breakpoint, and this is particularly the case for the urinary $S$-equol:daidzein ratio (Fig. 3). By contrast, plots of the $\log_{10}$-transformed $S$-equol:daidzein ratio for serum concentrations showed no clear demarcation, and this approach did not differentiate equol-producing status of an individual. The most likely reason for this is because the pharmacokinetics of daidzein and $S$-equol are markedly different (11,14), particularly with regard to renal clearance. Daidzein is more rapidly eliminated from the peripheral circulation than...
S-equol, and the dynamic changes in serum concentrations of the precursor and product will be amplified when the concentrations are expressed as a ratio. However, using urine measurements, dynamic changes in serum isoflavone concentrations are minimized, and it is this measurement that yields a more reliable classification of an equol producer. We have therefore designated a urinary log_{10} S-equol:daidzein ratio of greater than 1.75 as an indicator of an equol producer, and the advantage of this approach is that it is independent of the amount of daidzein ingested and of any the analytical differences among laboratories measuring isoflavones.

A striking finding from this study was the high frequency of equol producers observed within vegetarians, who were 4.25 times more likely to be S-equol producers as their nonvegetarian counterparts. Such association was of borderline significance, but it is likely that small sample size conditioned low statistical efficiency in the present study, as suggested by wide CIs. We retrospectively calculated that our study on 41 subjects attained a power of 0.36 in detecting a difference of the same magnitude as that observed between vegetarian habits, assuming a 2-sided risk of type I error of 0.05. The frequency of equol producers has been found to differ among populations (14). When equol was first identified more than 2 decades ago in human urine (2) and shown to be an intestinal bacterial metabolite derived from soy isoflavones (3,4), it was originally suggested that two-thirds of adults produced equol when consuming soy food (4). This frequency may have been overestimated due to the small sample size of only 6 adults studied or it has declined over the last 2 decades. More recent studies of Western populations have revealed a relatively lower frequency of equol producers, with the consensus of data indicating only about one-third of the adult population is capable of producing S-equol when fed soy foods (16,20,32,33). Studies from Japan have shown 55–60% of Japanese adults typically produce S-equol when consuming soy foods (17,18,34,35), and this striking difference in frequency is presumed to be accounted for by differences in the composition of the diet. Interestingly, the frequency of equol producers in young Japanese adults is much lower than in older Japanese adults and similar to that of Westerners (Professor Shaw Watanabe, Tokyo University of Agriculture, Japan personal communication). This difference has been claimed to be most likely due to the change in the Japanese diet, more evident in the younger Japanese. To our knowledge, there have been no previous reports of the frequency of equol production in vegetarians, but our finding that 59% of vegetarians are equol producers is similar to the frequency seen in Japanese adults (17,18,34,35) and would strongly implicate that differences in the composition of the diet may be crucial in facilitating intestinal bacterial metabolism of soy isoflavones. Identifying factors that govern equol production in adults has thus far proved elusive (10,14). It was previously reported that consuming a diet high in total carbohydrate and low in saturated fat is associated with equol production (16,32). This is supported by the observation that nonstarch polysaccharides enhance the conversion of daidzein to S-equol in an in vitro colonic model of cultured human fecal microflora by stimulating intraluminal fermentation (36). It is probable that vegetarian and Japanese diets provide more prebiotic components than a mixed omnivorous diet and this may be a key factor in the greater propensity to produce S-equol in these populations. However, several short-term dietary intervention studies of prebiotics and probiotics have failed to stimulate equol production in adults (37–40). Diet records were not obtained in this study, and, therefore, whether specific components of the diet were associated with equol production could not be determined. This was outside the scope of this work. History of soy food use was not recorded, but it is likely that many of the vegetarians were probably consuming soy foods as a protein source. It is doubtful that any prior soy food consumption could influence equol production based on the findings from a recent study showing no link between long-term soy food intake and ability to induce equol production in nonequol producers (41).

Finally, although there has been no previous association found between equol production and gender (42), within the limitations of the small sample size of this study, a male appeared to be 3.11 times more likely to be equol producer than a female.

In summary, we have described a more robust method of defining an equol producer based upon the log_{10}-transformed urinary S-equol:daidzein ratio after a standard 3-d challenge of soy foods containing isoflavones. This approach has advantages over relying on absolute serum or urinary S-equol concentrations because it exploits the precursor-product relation between daidzein and equol, thereby minimizing the errors in using specific threshold S-equol concentrations that are subject to large variance due to differences in dietary isoflavone intake, pharmacokinetics, and methodologies for measuring S-equol. In this study of 41 healthy adults, 59% of the vegetarians were identified as equol producers compared with only 25% of the nonvegetarians, suggesting differences in diet play a key role in determining an individual’s ability to make S-equol from ingested soy isoflavones.

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Literature Cited


