Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

FSH blocking antibody

Evidence Summary

Increases in FSH with menopause track with changes in body composition toward a state associated with age-related diseases. Preclinical studies suggest blocking FSH could mitigate these changes.

Neuroprotective Benefit: Changes in hormones during menopause, including FSH, are associated with vulnerability to cognitive decline, but the specific impact of FSH to this process hasn't been clearly established.

Aging and related health concerns: Elevated FSH around the menopausal transition has been associated with bone loss, increased fat mass, and atherosclerosis risk factors. FSH blocking interventions may have a defined therapeutic window.

Safety: FSH blocking antibodies have not yet been tested in humans. There is no evidence of toxicity with acute dosing in animal models. Long-term safety is unclear. The therapeutic profile is likely to change over the life course.

Availability: Research use	**Dose**: Not established	**Chemical formula:** N/A **MW:** N/A
Half-life: Hu6: 34-41 hours in mice, 7.5 days in humanized mice	**BBB**: Hu6 is minimally penetrant	
Clinical trials: None	**Observational studies**: High FSH levels are associated with osteoporosis, atherosclerosis, and metabolic syndrome.	

What is it?

Follicle stimulating hormone (FSH) is a gonadotropin hormone that is released by the pituitary gland [1]. It plays an important role in the production of eggs and sperm in the ovaries and testes, respectively. FSH levels vary over the course of the menstrual cycle in women. FSH is in a negative feedback loop with estrogen such that a rise in estrogen leads to a decline in FSH levels. Consequently, FSH levels rise during menopause due to the loss of estrogen. The change in FSH has been associated with a variety of physiological changes over the course of the menopausal transition, including changes in body composition, bone mass, and cognition [2]. Preclinical studies testing the use of exogenous FSH and FSH blocking antibodies in animal models suggest that there may be a direct role for FSH in these processes, due to the expression of the FSH receptor on cells outside of the reproductive system, including adipose tissue, the liver, bone cells, and the brain [3]. FSH blocking antibodies have not yet been clinically tested, so it is unclear the degree to which these mechanisms are also relevant in humans. There are also questions regarding whether there is an optimal window of therapeutic intervention as well as potential differences in the therapeutic profile between males and females.

Hu6 is a humanized anti-FSHβ antibody targeted to the FSH receptor binding epitope LVYKDPARPKIQK that binds two of the interacting residues, Y39 and A43, and has an affinity of ~ 7 nM [4]. It has been shown to block the binding of FSH to FSHR in *in vitro* assays and block the activity of FSH *in vivo* in preclinical models.

Neuroprotective Benefit: Changes in hormones during menopause, including FSH, are associated with vulnerability to cognitive decline, but the specific impact of FSH to this process hasn't been clearly established.

Types of evidence:

- 4 observational studies for FSH levels and cognitive impairment
- 2 observational studies for FSH levels and cognition
- 2 observational studies for FSH levels and measures of white matter
- 1 observational study for SNPs in FSHR and dementia risk
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

FSH blocking antibodies have not yet been tested in humans, but there is some evidence to suggest that FSH can impact brain structure and cognition. Brain imaging studies indicate that there are structural and functional changes in the brain over the course of the menstrual cycle. FSH levels vary over the four phases of the menstrual cycle, peaking during the early follicular phase. FSH levels fall during the transition from the early to late follicular stage, which is coupled by a rise in estrogen, brain derived neurotrophic factor (BDNF), an increase in hippocampal volume, and increased functional connectivity between the hippocampus and parietal lobe [5]. Studies are mixed as to whether cognitive abilities are also altered at a detectable level over the cycle. A longitudinal study of 2,411 mid-life women tracked changes in six cognitive domains over the menopause transition, which involves a decrease in estrogen and increase in FSH [6]. In this study, increases in FSH and luteinizing hormone (LH) were associated with worse performance on measures of immediate and delayed verbal episodic memory. In a study of 67 menopausal women, verbal cognitive measures, such as phonemic fluency and semantic fluency, were positively associated with estradiol and inversely associated with FSH levels [7]. These differences in cognitive performance were associated with changes in brain activation. Similarly, a study comparing 45 early menopausal women with 54 premenopausal women found that increases in FSH were associated with decreased working memory performance and decreased subcortical amygdala volume in early menopausal women [8]. FSH has also been associated with changes in white matter. In the KEEPS study (NCT00154180), decreases in FSH were associated with a lower rate of increase in white matter hyperintensity (WMH) volume in menopausal women taking transdermal 17β estradiol hormone

replacement therapy [9]. In older adults (age 50+) with HIV (n=79), there was an association between higher white matter volume and lower levels of FSH in women [10].

The association between FSH and dementia is unclear. An observational study (n=225) found that the AS/AS genotype for rs6165 (codon 307) and rs6166 (codon 680) in the FSHR gene was associated with decreased risk for Alzheimer's disease (AD) in women (Odds ratio [OR]: 0.36, 95% Confidence Interval [CI] 0.15 to 0.85) [11]. The S/S genotype (codon 680) has also been associated with a lower risk for osteoporosis and is implicated in having decreased FSHR activity. A study in 284 adults found that levels of FSH and LH were elevated in women with AD not taking estrogen [12], while a separate study found a decrease in estrogen, but no significant differences in FSH or LH between postmenopausal women with dementia relative to controls [13].

A complicating factor in these studies is that changes in FSH levels are coupled with changes in other hormones over the menstrual cycle and menopausal transition. This makes it difficult to tease apart the exact contribution of FSH. Due to differences in study design and population, there have been mixed results across studies as to whether cognitive changes in menopausal women can be attributed to FSH, estrogen, or other hormones. It is further complicated by the fact that these hormones can influence one another. The evidence suggests that the changes to the brain are related to the changes in the entire milieu of reproductive hormones. Some studies suggest that estrogen is a modifier of the relationships between FSH and various phenotypes [14]. For example, one cross-sectional study including 282 postmenopausal women found that an elevated ratio of FSH to estradiol (≥1.94) was associated with increased risk for mild cognitive impairment (MCI) (OR: 1.057, 95% CI 0.789 to 1.416) [15].

Although the age-related increase in FSH is most prominent in postmenopausal women, FSH levels have also been shown to increase with age in men at a rate of about 3% per year [16]. A cross-sectional study of 576 elderly (>age 65) men in China found that men with probable AD showed lower levels of free testosterone along with higher levels of FSH and LH, relative to those with normal cognition [17]. A similar association was seen in a cohort of 210 elderly men in the UK [18], while another study found no association [12]. Androgen deprivation therapy is used in the treatment of prostate cancer. One form of it involves the use of gonadotropin-releasing hormone (GnRH) agonists, which transiently increase the production of FSH and LH, ultimately leading to their downregulation [19]. A retrospective cohort study of 209,722 men with prostate cancer found that the use of GnRH agonists was associated with increased risk for neurodegenerative disease (Relative risk [RR]: 1.47, 95% CI 1.30 to 1.66) [20].

These studies suggest that changes in gonadal hormones may impact the risk for age-related cognitive decline and dementia, however, it has not been clearly established whether FSH plays a dominant role,

or whether it would need to be modulated in combination with other factors. Additionally, there is evidence from hormonal replacement studies to suggest that there may be an optimal window for therapeutic intervention around the time of the menopausal transition. It is unclear if the potential benefit of FSH blockers would also be time limited. Since FSH levels start rising during the perimenopausal period, which is earlier than the period that estrogen falls, the optimal therapeutic window may be shifted for FSH blockers.

Human research to suggest benefits to patients with dementia:

There is no evidence to date that reducing FSH levels can impact disease progression in dementia patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's disease: POTENTIAL BENEFIT (Preclinical)
Treatment with an anti-FSHβ antibody prior to symptom onset was found to reduce brain pathology in AD mouse models [21]. In 3.5-month-old female 3x-Tg mice, treatment with anti- FSHβ (200 µg every 2 days i.p.) for eight weeks starting four days after ovariectomy led to a reduction in brain levels of Aβ and tau. A reduction in Aβ levels was also seen with anti- FSHβ treatment (120 to 150 µg i.p. 5 days/week) for four months starting at five months of age in male APP/PS1 mice. Similar to the antibody, treatment of ovariectomized 3xTg female mice with FSH siRNA protected against neuronal loss and improved memory performance on the Morris water maze. The neuroprotective effect stems from the antibody's ability to block the activation of C/EBPβ by FSH. C/EBPβ activates arginine endopeptidase (AEP), a δ-secretase enzyme that cleaves amyloid precursor protein to generate Aβ and tau aggregates. Based on cell culture, FSH phosphorylates AKT, ERK1/2 and SRPK2, which leads to the activation of C/EBPβ. Systemic injection of recombinant FSH into 3x-Tg female mice for three months induced increases in brain levels of activated C/EBPβ and AEP. A similar effect was seen in female APP-knock-in mice, along with the accumulation of Aβ in the brain. Together these studies suggest that elevated FSH may activate pathways which promote the generation of Aβ-related pathology. They also suggest that anti-FSHβ may be most beneficial during the period when FSH levels begin to rise, such as during the menopausal transition, and during a preclinical stage prior to the onset of AD symptoms.

APOE4 interactions: Not established.

Aging and related health concerns: Elevated FSH around the menopausal transition has been associated with bone loss, increased fat mass, and atherosclerosis risk factors. FSH blocking interventions may have a defined therapeutic window.

Types of evidence:

- 6 observational studies for FSH levels and bone loss/osteoporosis
- 4 observational studies for FSH levels and markers of atherosclerosis
- 4 observational studies for FSH levels and measures of body fat
- 3 observational studies for FSH levels and blood lipids
- 3 observational studies for FSH levels and insulin resistance
- Numerous laboratory studies

Longevity: FSH INCREASES WITH AGING

FSH has been implicated as a longevity-associated hormone such that lower levels of FSH may foster a longer lifespan [3]. FSH levels increase with age in both men and women. Ames mice, which have a deficit in pituitary function, and growth hormone deficient mice have extended lifespans [22]. Among the many hormonal alterations in these animals is a decrease in FSH levels, though it has not been established what role, if any, FSH plays in the longevity of these animals.

Osteoporosis: POTENTIAL BENEFIT (Preclinical)

There are numerous observational studies suggesting a link between FSH levels and the risk for osteoporosis. The Study of Women's Health Across the Nation (SWAN) examined the relationship between bone mineral density and variations in reproductive hormone levels in 2,336 from an ethnically diverse cohort of pre- and perimenopausal women aged 42–52 years old [23]. **Serum FSH levels were found to be inversely associated with bone mineral density** in the lumbar spine and femoral neck region. For each successive quartile in FSH levels, there was an approximately 0.5% decrease in bone mineral density in the lumbar spine. In this study, the association was seen with serum FSH, but not with serum estradiol, testosterone, or sex hormone binding globulin (SHBG). The Buffalo OsteoPerio Study including 675 postmenopausal women found that the odds of low bone mass (i.e. osteoporosis) at the femoral neck (OR: 2.98, 95% CI 1.86 to 4.77) and at the total hip (OR: 1.74, 95% CI 1.06 to 2.84) were elevated in women in the highest tertile of serum FSH relative to those in the lowest tertile [14]. However, the association between FSH and bone mass was modified by estradiol, such that women with osteoporosis had the highest serum FSH levels (63.5 ±29.1 mIU/mL) and lowest estradiol levels relative to women with normal bone mass (FSH 50.4 ± 27.3 mIU/mL). In women with higher estradiol levels

(> 19.8 pg/mL), those in with the highest FSH showed evidence for reduced bone mass, but there was no clear association in those with intermediate FSH levels, suggesting that a high estrogen environment may mitigate the effect of FSH. The complexity of the relationship between FSH and bone mass was further investigated in an analysis of data from 3,743 pre- and postmenopausal women (aged 35-60) from the National Health and Nutrition Examination Survey (NHANES) [24]. Menopausal changes in bone mineral density follow a non-linear trend. Bone loss typically starts two to three years prior to the last menstruation, accelerates during the two years following the last menstruation, and then the rate of loss slows down. The study found that there was a significant non-linear relationship between serum FSH levels and the risk for osteoporosis in postmenopausal women. High serum FSH levels were associated with lower bone mineral density in the lumbar spine and femoral neck, as well as a slightly increased risk for osteoporosis (OR: 1.004, 95% CI 1.000 to 1.008, P = 0.050). The increased risk for osteoporosis was present with serum FSH levels between 30 IU/L and 120 IU/L. Consistent with this finding, a separate study including 638 women aged 20 to 50 found that levels of FSH >30 IU/L were associated with the period of perimenopause and with increased levels of bone turnover markers [25]. The non-linear relationship is hypothesized to stem from the dynamic relationship between FSH and estrogen during the menopausal transition [24]. The perimenopausal period of bone loss could stem from the elevation of FSH but is tempered by high estrogen levels. The decline in estrogen during menopause facilitates the acceleration of bone loss, and then the process begins to stabilize as the body adapts to the new hormonal landscape. The complexity of this dynamic likely explains why the link between FSH and bone loss has not been seen consistently across studies [14]. In general, the link has primarily been detected in large studies, and absent in small studies, suggesting that small studies may not be adequately powered to detect this relationship.

A further complexity stems from the association between osteoporosis and muscle mass. Low muscle mass is associated with higher risk for osteoporosis, and FSH also shows a complex relationship with body mass in that it has been inversely associated with both lean mass and fat mass [26]. As a result, the association between bone loss and FSH may be partially mediated by the association between lean mass and FSH. FSH may have both direct effects on bone loss through its effects on bone tissue, as well as indirect effects stemming from the modulation of body composition [3].

There is some evidence to suggest that the interplay between FSH and other reproductive hormones may also impact the risk for osteoporosis in older men. In a cross-sectional study of 199 men in China aged 41 to 82, FSH levels increased with age [27]. Levels of FSH were higher in men with osteoporosis (11.45 IU/L, 95% CI 7.97 to 19.4 IU/L) relative to those with normal bone mass (9.35 IU/L, 95% CI 6.94 to 13.7 IU/L). There was a 50% increase in the risk for osteoporosis or osteopenia with each standard deviation increase in FSH levels (OR: 1.509, 95% CI 1.015 to 2.242) in an adjusted analysis. The risk for

osteoporosis was also associated with changes in body composition, namely an increase in marrow fat and erector muscle fat content. A study assessing the relationship between FSH and osteoporosis in 446 men (≥ 50 years old) and 349 postmenopausal women with type 2 diabetes found that the risk for osteoporosis was more strongly associated with estradiol in men and with FSH in women [28]. Men with low estradiol (< 87.96 pmol/L) showed a 1.6-fold higher risk for osteoporosis, while women with lower FSH levels (< 41.17 IU/L) had a lower risk (0.6-fold).

There is evidence from preclinical studies to support a direct role for FSH in bone loss, which may be prevented through the use of anti-FSH therapy. Osteoclasts express a Gi2α-coupled form of the FSH receptor [29]. The activation of the receptor by FSH leads to the activation of pathways that promote osteoclastogenesis and bone reabsorption activity. Elevated FSH has been implicated in mediating hypogonadal bone loss in mice. In ovariectomized female rats, immunization with a GST-FSHβ fusion protein antigen improved mechanical and structural bone parameters and significantly prevented trabecular bone loss [30]. The antisera from the immunized animals blocked FSH-induced osteoclast differentiation in cell culture. The humanized FSH-blocking antibody, MS-Hu6 (7 μg/day, 5 days/week for 8 weeks) significantly increased fractional bone volume, trabecular thickness, mineral apposition rate, and bone formation rate in male mice [31]. Treatment with MS-Hu6 (100 μg/day, for 4 weeks and then 50 μg/day for another 4 weeks) improved total body and femoral bone mineral density and cortical thickness in female ovariectomized mice. FSH may also promote bone loss through the promotion of inflammation. Periapical periodontitis involves the recruitment of inflammatory cells and osteoclasts into the root canal system, leading to bone reabsorption [32]. The enhancement of bone loss of periapical lesions following ovariectomy in rats was prevented by treatment with the FSH inhibitor leuprorelin. FSH potentiated the induction of toll-like receptor (TL4) inflammatory signaling following exposure to *Porphyromonas gingivalis* LPS, which may be a driver of inflammatory bone loss.

Atherosclerosis: ELEVATED FSH IS ASSOCIATED WITH SUBCLINICAL ATHEROSCLEROSIS AND ELEVATED LDL-C IN EARLY MENOPAUSAL WOMEN

Cardiovascular risk increases in women starting in perimenopause [33]. Several observational studies have examined the relationships between changes in cardiovascular risk factors and hormones over the course of the menopausal transition. Increases in FSH have been associated with risk factors and markers of atherosclerosis in various studies, and preclinical studies provide evidence for a mechanistic role in lipid homeostasis.

Several studies have identified associations between FSH levels with markers of subclinical atherosclerosis which were independent of estrogen. In a prospective study of 126 asymptomatic pre-,

peri-, and postmenopausal women (mean age 50), there was a shift toward more calcified coronary artery plaques in postmenopausal women [33]. Based on a coronary heart disease model, the 10-year Framingham risk score, there was a positive association between plaques and testosterone levels, and an inverse association with sex hormone–binding globulin (SHBG). Estrogens did not show an association with subclinical atherosclerosis, whereas increased FSH levels were associated with an increased number of aortic plaques. Similarly, a study in 145 pre- and postmenopausal women (ages 45-65) found a positive association between carotid intima-media thickness, a measure of subclinical arterial plaque buildup, and FSH levels [34]. A cohort of 1,552 women undergoing the menopausal transition that were monitored as part of the SWAN study underwent carotid ultrasound assessments to assess the relationship between subclinical atherosclerosis and hormonal trajectories [35]. Estradiol and FSH trajectories over the course of the menopausal transition were associated with measures of subclinical atherosclerosis. Protection from atherosclerosis following menopause was associated with high estradiol prior to the transition followed by low estrogen after, as well as with a low rise in FSH over the course of the menopausal transition. The study authors posit that a high lifetime exposure to FSH or rapid elevation may negatively impact the vasculature. However, a study including 587 postmenopausal women (age 53-73) from the Kuopio Ischemic Heart Disease Risk Factor Study observed an inverse association between FSH levels and carotid artery intima-media thickness, which was most prominent in the oldest subgroup (age 64-73), and not associated with body mass index or estrogen [36]. Together, these studies suggest that high levels of FSH during the premenopausal, perimenopausal, and menopausal transition periods may promote vascular changes that increase the risk for atherosclerosis, whereas the impact of FSH may lessen once hormones have stabilized during the late postmenopausal period. Due to changes in the hormonal milieu following menopause, FSH could potentially have some protective effects, or higher FSH could be associated with a protective hormonal environment. For example, the production of FSH is stimulated by activins, which have been associated with atheroprotection, such that in late postmenopausal women, the protective association with FSH could be mediated by its relationship with activins [36].

The relationship between FSH and atherosclerosis may be related to the associations between circulating levels of FSH and lipids. Women with premature ovarian failure and a serum FSH level >40 I/U were found to have LDL-C levels that were 41.2% higher than healthy premenopausal women, while women with premature ovarian failure and serum FSH levels (25- 40 IU/L) had LDL-C levels that were 24.8% higher [37]. In a study including 154 pre-menopausal and 124 peri-menopausal women, levels of FSH, total cholesterol and LDL-C were higher in peri-menopausal women [38]. Furthermore, the increases in total cholesterol and LDL-C were positively associated with the increase in FSH. In a study of 400 postmenopausal women in China (age 42–60), high baseline FSH levels (≥78.3 IU/L) were associated

with higher serum total cholesterol and LDL-C [39]. Levels of total cholesterol (by 3.7%) and LDL-C (by 4.4%) decreased following hormone replacement therapy (1 mg estradiol valerate tablets per day) for 12 months. When stratifying by response rate, the women who showed significant reductions in serum cholesterol parameters belonged to the group exhibiting a ≥ 30% reduction of FSH levels. In postmenopausal women (n=588) in the Kuopio Ischemic Heart Disease Risk Factor Study, FSH was positively associated with levels of total cholesterol and LDL-C. Consistent with the finding that higher FSH was associated with less atherosclerosis primarily in the older cohort, the associations between FSH and serum lipids were most prominent in the younger cohort (age 53–62). These studies suggest that elevations in FSH may be most detrimental to the lipid profile early during the menopausal transition.
In a mouse model of atherosclerosis (ApoE-/- fed a high fat diet), treatment with FSH led to an enlargement of aortic plaques which was coupled with a decrease in collagen and an increase in macrophages, suggestive of plaque instability [40]. In carotid plaque and blood samples from human patients (n=126) five differentially expressed genes were found to be correlated with FSH. The inflammatory molecules NOS2, IL-1β, and IL-6 were elevated in undifferentiated macrophages, suggesting the FSH may promote the differentiation of macrophages into a pro-inflammatory subtype that can exacerbate atherosclerotic progression.
The effect on serum cholesterol levels may be mediated by the effect of FSH on hepatic cholesterol clearance, based on preclinical studies. The FSH receptor was found to be expressed on human hepatic cells. FSH treatment inhibited the expression of the LDL receptor in cultured liver cells, which could reduce the uptake of LDL-C, resulting in higher circulating levels. Serum cholesterol levels were lower in ovariectomized mice lacking FSHR. These mice were also partially protected against high-cholesterol diet-induced hypercholesterolemia. The expression and activity of HMGCR, the rate-limiting enzyme in cholesterol biosynthesis, was increased in the livers of mice treated with FSH, suggesting that FSH plays a role in liver *de novo* cholesterol biosynthesis which is mediated by the activation of Gi2α/β-arrestin2/Akt pathway in response to FSHR activation. Treatment with an anti-FSHβ antibody (100 µg/day i.p.) for four weeks protected against increases in serum cholesterol in ovariectomized mice. Antibody treatment for eight weeks also reduced serum and hepatic cholesterol levels in wildtype mice. Additionally, anti-FSHβ treatment prevented the FSH-mediated accumulation of hepatic cholesterol in LDLR deficient mice.
Together, these suggest that FSH can promote the synthesis of cholesterol in the liver and reduce uptake, resulting in elevated levels of circulating cholesterol, as well as affect immune cell activation, which can contribute the development of atherosclerotic plaques. The impact of this pathway likely depends on the relative levels of FSH in relation to other hormones and factors that can impact lipid

metabolism, which may explain why elevated FSH appears to have an outsized impact on atherosclerotic risk under particular conditions.

Obesity: POTENTIAL BENEFIT (Preclinical)
The relationship between FSH and body mass is complex, which has resulted in seemingly contradictory findings across studies. There is a shift in body composition during menopause toward a reduction in lean mass and an increase in fat mass, particularly visceral fat. Visceral fat is pro-inflammatory and is associated with metabolic syndrome. A study in 69 women between the ages of 45 and 60 found that postmenopausal women had larger total fat mass, visceral fat mass, leukocyte immune cells, and pro-inflammatory cytokines (IL-1β, IL-6, TNFα), relative to premenopausal women [41]. The increase in leukocytes was associated with higher visceral fat, while the increase in inflammatory cytokines was associated with elevated FSH. The associations were weakened with adjustment, suggesting that there are multiple factors at play in mediating the inflammatory response in postmenopausal women.
The association between FSH and metabolic measures such as obesity, type 2 diabetes, and metabolic syndrome appear to be heavily influenced by levels of estrogen and likely by other hormones as well. As a result, the observed associations with FSH may vary between pre- and postmenopausal women in conjunction with the changes in other reproductive hormones. The associations may also be influenced by adiposity because adipose tissue is estrogenic.
In the SWAN cohort of 2,930 pre- and perimenopausal women (aged 42–52), serum levels of FSH and estradiol were found to be highly variable in perimenopausal women, and this was partially mediated by differences in body size [42]. In premenopausal women, a high body mass index (BMI) was associated with lower serum estradiol levels, but over the course of the menopausal transition, the association reverses such that a higher BMI correlates with higher estradiol levels [43]. The levels of FSH are reduced in both pre- and postmenopausal women with higher BMI, but the association is much stronger following the menopausal transition. This pattern emerges because over the course of the menopausal transition, adipose tissue becomes the predominant producer of estrogen, and estrogen is in a negative feedback loop with FSH. As a result, FSH levels are low because fat levels are high. This effect makes it difficult to determine the potential impact of FSH itself on adipose tissue. Additionally, BMI is a crude measure which does not differentiate between lean and fat mass.
Changes in body composition and hormones over the course of the menopausal transition were analyzed in a cohort of 543 women from the SWAN study who were tracked longitudinally [44]. Over the six-year observation period, there were annual increases in body weight, fat mass, and waist circumference, along with decreases in height and skeletal muscle mass. The changes in fat mass, waist circumference, and muscle mass were associated with the changes in FSH levels. Other studies have also

reported associations between higher FSH levels with measures of central obesity, which is an indicator of increased visceral fat [3].

Preclinical studies suggest that FSH may impact the accumulation of fat through its ability to regulate lipogenesis. The FSH receptor is expressed on adipocytes, which makes them responsive to changes in FSH levels [45]. Treatment of immortalized dedifferentiated brown adipocytes with FSH inhibited expression of Ucp1, which is a master regulator of adipocyte beiging and thermogenesis. This effect was prevented by treatment with a polyclonal antibody raised against Fshβ (LVYKDPARPNTQK). The antibody (200 µg/day, i.p) did not protect against weight gain in response to a high fat diet in wildtype mice, but did shift the profile to a lower increase in fat mass relative to lean mass, such that the treated mice showed lower levels of visceral and subcutaneous fat [45]. The treated mice showed increased energy expenditure and a higher resting metabolic rate. The effect was not driven by an increase in activity levels, but rather by increased adipose tissue beiging and thermogenesis. Antibody treatment (200 or 400 µg/day, i.p) protected against gains in fat mass in ovariectomized mice, and at lower doses (100 µg/day, i.p) reduced abdominal fat mass in wildtype mice fed normal chow. Plasma levels of glucose, cholesterol, triglyceride, or free fatty acids were not affected by antibody treatment in these mice. FSH antibody treatment increased the expression of genes associated with adipose tissue beiging as well as the increase in mitochondrial density needed to drive thermogenesis in adipocytes.

However, there are numerous observational studies showing an association between low FSH levels and worse outcomes in people with type 2 diabetes, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD) in postmenopausal women [2]. Although the effect appears to be partially mediated by the ability of fat-derived estrogen to inhibit FSH, the association persists in many studies, even after controlling for obesity and estrogen. This suggests that under certain conditions, FSH levels may rise in conjunction with the induction of protective factors. It is not clear whether the FSH itself offers benefit, or if the increase in FSH is simply indicative of a change in another protective factor. Several studies suggest that some of the protective effects may be driven by an association between FSH and the adipokine, adiponectin. Adiponectin promotes insulin sensitivity, such that low levels of adiponectin can be a marker of insulin resistance. A study in 408 postmenopausal women (age 40-65) found that in women without breast cancer, FSH levels were positively associated with adiponectin levels and inversely associated with a marker of insulin resistance (HOMA-IR) [46]. Similarly, a study including 219 postmenopausal women (age 45-71) found that the odds for metabolic syndrome were highest in women with the lowest quartile of FSH (OR: 1.32, 95% CI 1.09 to 1.75) [47]. FSH levels were positively associated with adiponectin and inversely associated with insulin resistance (HOMA-IR). In a prospective five-year study in 114 postmenopausal women (age 45-60), a one-standard deviation decrease in the z-score FSH concentration was associated with a nearly three-fold increased risk (OR: 2.83, 95% CI 1.3 to

6.0) for prediabetes, and a five-fold increased risk for insulin resistance and diabetes, across a variety of adjusted models [48]. The authors speculate that this could be related to changes in the levels of activins and follistatin, and/or that differences in the posttranslational modifications of FSH, such as sulfonation, after menopause may impact its function, resulting in different effects in pre/peri- and postmenopausal women.
Together these studies suggest that FSH may impact adipose tissue, but the overall effect may depend on the total hormonal milieu and metabolic state. The evidence for a protective effect in blocking FSH appears strongest during the period of the menopausal transition.

Osteoarthritis: POTENTIAL BENEFIT (Preclinical)
FSH was shown to exacerbate inflammation when injected into the knee in a mouse model of osteoarthritis (destabilization of medial meniscus) [49]. FSH treatment induced the de-differentiation of chondrocytes and promoted an inflammatory response via the inhibition of cAMP/PKA and MKK4/JNK signaling.

Safety: FSH blocking antibodies have not yet been tested in humans. There is no evidence of toxicity with acute dosing in animal models. Long-term safety is unclear. The therapeutic profile is likely to change over the life course.

Types of evidence:

- Several laboratory studies

FSH blocking antibodies have not yet been clinically tested. Radiolabeled Hu6 antibody (89Zr-MS-Hu6) (250 µCi) was found to be distributed to the liver, bone marrow, subcutaneous adipose tissue, visceral white adipose tissue, and brown adipose tissue in mice [31]. Limited amounts of labeled Hu6 were detected in the brain after 72 hours, which was indicative of low brain penetration (0.05–0.1%). Following i.v. administration of AF750-MS-Hu6 (200 µg), labeled Hu6 was detected in the liver, kidney, fat depots, bone, and brain in mice. In male Cynomolgus monkeys, 89Zr-MS-Hu6 was administered as a single bolus dose (1.3 mg, ~1.3 mCi) via the tail vein. Hu6 was detected via PET imaging at high concentrations in the liver and gallbladder, and at lower levels in the kidney, spleen, fat depots, bone marrow, and the brain [31]. The 89Zr-MS-Hu6 did not show any significant effects on changes in heart rate, respiratory rate, mean arterial blood pressure, systolic or diastolic blood pressure, or rectal temperature with 100 minutes of administration, and blood draws taken up to five days later did not

show changes in serum biochemical parameters, including glucose, triglycerides, total protein, calcium, phosphorus, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, creatinine, BUN, or albumin. Treatment with FSH blocking antibodies phenocopies mice that are haploinsufficient for the FSH receptor (FSHR+/-). FSHR+/- mice show normal lifespans relative to wildtype mice. Hu6 was found not to significantly cross react with a panel of relevant antigens including cardiolipin, lipopolysaccharide, double- and single-stranded DNA, insulin, human albumin, and flagellin, but did show some cross-reactivity towards hemocyanin and baculovirus particles, though not at a level that is expected to be clinically meaningful.

Due to its role in ovarian function, chronic blocking of FSH in healthy premenopausal women is likely to negatively impact fertility [1]. It is unclear whether they would also impact the fertility of men. However, the long-term impacts of reducing FSH in older men and postmenopausal women are unclear. Since GnRH agonists and antagonists impact pituitary hormones other than just FSH, it is unclear whether their safety profiles provide a reliable guide toward the potential effects of selective FSH blockers. Ultimately, their safety will likely depend on the age/stage of life in which they are administered, as well as the dosing frequency/duration.

Drug interactions: Interactions have not been established, but FSH blockers may interact with drugs that affect pituitary function (Drugs.com), and are expected to be contraindicated in premenopausal women.

Sources and dosing:

The humanized anti-FSHβ antibody, Hu6 is being developed in an academic lab at the Icahn School of Medicine at Mount Sinai and has not yet undergone clinical testing.

Research underway:

The humanized anti-FSHβ antibody, Hu6, is currently in preclinical development, and there are no clinical trials for selective FSH blockers at this time.

Search terms:

Pubmed, Google: FSH

- Alzheimer's disease, neurodegeneration, cognition, osteoporosis, obesity, metabolic syndrome, atherosclerosis, aging, lifespan

References:

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