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COMBINED THERAPEUTIC EFFECT OF DIETARY SELENIUM AND VITAMIN E ON MANIFESTED VESD* SYNDROME IN WEANED PIGS**

By

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HAKKARAINEN, J., P. LINDBERG, G. BENGTSSON and L. JÖNSSON: *Combined therapeutic effect of dietary selenium and vitamin E on manifested VESD syndrome in weaned pigs.* Acta vet. scand. 1978, *19*, 285—297. — By using a therapeutic dietary supplementation in pigs, which had developed the vitamin E and selenium deficiency (VESD) syndrome, the same amounts of α-tocopheryl acetate and selenium were found to be effective as under prophylactic conditions. The experiment thus supported the conclusions that the addition of 5 mg DL-α-tocopheryl acetate/kg and 135 μg selenium/kg to a diet, which contained only traces of vitamin E and selenium, represents a level of minimal requirement. Glutathione peroxidase activity in blood serum was used to evaluate the selenium status in pigs. A modified method for determination of tocopherol in fat tissue was described. The addition of 15 mg α-tocopheryl acetate/kg diet was demonstrated to be sufficient to maintain the tocopherol stores in body fat at an unchanged level.

dietary tocopherol; selenium; therapy; pigs; serum glutathione peroxidase; tissue fat tocopherol.

The requirement of selenium and α-tocopherol in weaned pigs has been investigated recently by us (*Bengtsson et al.* 1976, 1978a, b, *Hakkarainen et al.* 1978a) and others (*Trapp et al.*

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* Vitamin E and Selenium Deficiency.

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1970, *Wastell* 1970, *Ewan* 1971, *Sharp et al.* 1972a, b, c, *Groce et al.* 1973, *Piper et al.* 1975, *Van Vleet et al.* 1975). The addition of 135 μg selenium/kg diet was found to be sufficient to prevent the vitamin E and selenium deficiency (VESD) syndrome, when the content of α-tocopherol was about 6 mg/kg (*Hakkarainen et al.* 1978a). These amounts of the 2 supplements were inadequate when administered separately (*Bengtsson et al.* 1978a, b).

In previous works the requirements for selenium and/or tocopherol in weaned pigs have been demonstrated by prophylactic experiments by using a basic diet, which contained only traces of selenium and tocopherol (*Bengtsson et al.* 1974, 1978a). The basic diet was supplemented with increasing amounts of selenium and/or tocopherol in order to prevent the development of the VESD syndrome (*Bengtsson et al.* 1978a, b, *Hakkarainen et al.* 1978a).

However, from a practical point of view, it must be ever so important to establish the supplementation levels of selenium and tocopherol which are needed by the pigs to recover from the VESD syndrome. In consequence the present experiment was designed to use therapy instead of prophylaxis. Thus, the pigs were first given the basic diet only in order to allow the VESD syndrome to develop. Selenium and vitamin E were then added and the disappearance of symptoms was studied.

MATERIAL AND METHODS

The preparations and the composition of the basic diet have previously been reported (*Bengtsson et al.* 1974, 1978a). A selenium deficient milk casein from selenium deficient cows was used as the protein source in a vitamin E-deficient diet for pigs. The basic diet was composed of low-selenium casein 17 %, wheat starch 53 %, sugar 20 %, cellulose 3 %, molecular-destilled cotton-seed oil 3 %, and a mineral and vitamin mixture. This diet contained 8.0 ± 0.9 μg selenium/kg DM (mean ± 1 s) and 2.5 mg tocopherol (1.4 mg α-tocopherol and 1.1 mg γ-tocopherol)/kg DM as determined according to *Lindberg* (1966, 1968).

Twenty-four weaned pigs were obtained from 3 different sows. They were divided into 4 groups. The basic diet was introduced on day 0 and fed to all groups until they showed clear clinical VESD lesions, i. e. cutaneous microangiopathy (MAP) (Table 2), pathological serum ASAT (Table 3) and low-gluta-

thione peroxidase (Table 4) values. The control group, i. e. the pigs in Group 1, were allowed to die spontaneously without supplementation of the basic diet with selenium and tocopherol. After the appearance of clinical VESD symptoms the pigs in Groups 2, 3 and 4 were subjected to a therapeutic treatment in the form of selenium and tocopherol supplementation of the basic diet. The treatment in Groups 2 and 3 was introduced on day 32, and in Group 4 on day 42. The experimental plan in detail appears in Table 1.

Serum aspartate aminotransferase (ASAT, GOT, EC 2.6.1.1.) was determined as recommended by the *Committee on Enzymes* of the Scandinavian Society for Clinical Chemistry and Clinical Physiology (1974). The normal upper limit of serum ASAT (mean + 2 s) was accepted to be 100 i. u./l (*Wretlind et al.* 1959, *Ekman & Edqvist* 1974).

Glutathione peroxidase (GSH-Px, EC 1.11.1.9.) activity was determined in blood serum at pH 7.4 and 25°C with a coupled test system according to *Paglia & Valentine* (1967), cumene hydroperoxide being used as substrate (*Little et al.* 1970, *Hakkarainen et al.* 1978b).

All pigs were necropsied within 10 hrs. after death. Tissues were fixed in 10 % neutral buffered formalin and processed for paraffin tissue sections according to conventional methods. Sections were stained with hematoxylin and eosin, Masson's trichrome, Mallory's phosphotungstic acid-hematoxylin (PTAH), periodic acid Schiff (PAS) and martius-scarlet-blue (MSB).

Determination of tocopherol in fat tissue

Samples of subcutaneous and abdominal fat were collected at the necropsies for determination of tocopherol. They were stored at —24°C until analyzed. About 3 g of the fat tissue was homogenized with 35 ml of acetone in a glass homogenizer. The homogenate was filtrated. The fat content of the filtrate was determined by weighing. Four ml of the solution was pipetted into each of 4 test tubes. One hundred µl tocopherol standard (50 µg/ml) was added to 2 of the test tubes. The acetone was evaporated with nitrogen over a 75°C water bath. Three ml of ethanol, purified by distillation over KOH, was added. One ml of ethanol, containing 5 % pyrogallol, was added. One ml of 5 % KOH was added. After each addition the contents of the

tubes were briefly mixed on a Vortex mixer. The tubes were then left in a 60°C water bath for 5 min. The samples were cooled in ice water. Four ml of spectrograde hexane was added, shaken for 2 min. on the Vortex mixer, and the mixture was centrifuged for 2 min. One ml of the hexane phase was mixed with 3 ml of ethanol. Fluorescence was read on a Perkin Elmer spectrofluorometer MPF 2A (excitation at 295 nm, reading at 340 nm) (*Duggan* 1959). The error of the method was calculated to be 0.96 μg/g in subcutaneous fat, giving a coefficient of variation of 4.9 % ($n = 17$).

RESULTS AND DISCUSSION

It has been shown previously, by using a basic diet identical with that in the present work, that a combination of 5 mg α-tocopheryl acetate and 135 μg selenium/kg diet will prevent the development of the vitamin E and selenium deficiency (VESD) syndrome in weaned pigs (*Hakkarainen et al.* 1978a). Neither 5 mg α-tocopheryl acetate nor 135 μg selenium/kg diet alone are effective protection, nor is a combination of 5 mg α-tocopheryl acetate and 45 μg selenium/kg.

The present experiment was performed to find out whether these prophylactical doses of vitamin E and selenium were also effective in therapy of the clinically manifested VESD syndrome. Thus, this syndrome was allowed to develop before the additives were mixed into the food, and the rate of recovery was subsequently observed. This mode of procedure implies a new approach to elucidate deficiency conditions and to establish requirements of essential nutritients.

The therapeutic supplementation with 5 mg DL-α-tocopheryl acetate plus 135 μg selenium/kg diet (Group 2), and with 15 mg DL-α-tocopheryl acetate plus 135 μg selenium/kg diet (Group 3) both resulted in recovery. The pigs improved rather rapidly. The cutaneous microangiopathy (MAP) reactions disappeared (Table 2) and the serum ASAT values were normalized (Table 3). In contrast, the supplementation with 5 mg α-tocopheryl acetate plus 45 μg selenium/kg diet (Group 4) was insufficient. Thus, the results of therapy are in aggreement with those obtained by prophylactic treatment, i. e. the prophylactical doses were also effective in therapy of the manifested VESD disease.

It was found even in the present study that skin maculae is a valuable diagnostic and prognostic criterion. The symptoms of

Table 1. Experimental plan and body growth of pigs. Pigs 49 to 57 (Sow 1075) were born on December 9, Pigs 58 to 66 (Sow 1077) on December 10 and Pigs 67 to 76 (Sow 1079) on December 10, 1975. The pigs were weaned on February 5 = day —1. The basic diet was introduced on February 6 = day 0. The basic diet contained 8.0 ± 0.9 μg Se/kg and 2.5 mg tocopherol (1.4 mg α-tocopherol)/kg. The therapy, i.e. the additives of selenium and tocopherol were included as noted in column "treatment". Mean survival time of Group 1 was 34.4 ± 7.9 days (mean ± 1s).

Group	Treatment	Pig No.	Sex	Body wt on day —1 kg	Died (d) or euthanized (e) on day	Body wt on day of death, kg	Av. daily gain (g)
1	None	50	m	10.5	29 d	19.6	314
		56	m	13.5	31 d	24.0	339
		58	m	24.0	44 d	37.0	295
		63	f	24.0	43 d	34.5	244
		65	f	20.0	44 d	28.5	193
		70	f	11.5	28 d	16.2	168
		72	m	13.0	25 d	17.3	172
		75	f	16.5	31 d	21.0	145
2	Days 0—31: None	49	f	15.5	60 e	40.5	417
	From day 32: 5 mg DL-α-tocopheryl acetate/kg[a] and 135 μg Se (as sodium selenite)/kg food	51	m	16.0	60 e	38.5	375
		54	m	16.0	60 e	43.5	458
		57	m	15.0	60 e	38.0	383
		68	m	14.5	60 e	34.5	333
		74	f	11.5	60 e	27.5	267
3	Days 0—31: None	52	f	12.5	48 e	25.0	260
	From day 32: 15 mg DL-α-tocopheryl acetate/kg[a] and 135 μg Se (as sodium selenite)/kg food	53	f	17.0	48 e	35.0	375
		55	m	18.5	48 e	31.0	260
		67	m	17.5	48 e	37.0	406
		73	f	14.5	48 e	28.0	281
		76	m	15.5	48 e	28.0	260
4	Days 0—41: None	59	f	18.5	47 d	26.0	125
	From day 42: 5 mg DL-α-tocopheryl acetate/kg[a] and 45 μg Se (as sodium selenite)/kg food	60	f	21.0	60 e	36.5	258
		64	m	18.0	60 e	36.5	308
		66	m	27.0	60 e	40.5	225

[a] Vitamin E dry powder 25 % (Merck Art. 501618).

cutaneous microangiopathy (MAP) appear at about the same time as the serum ASAT values begin to exceed the upper normal border line. The occurrence of cutaneous MAP (Table 2) was also correlated to necropsy findings characteristic for the VESD syndrome (Table 6).

Table 2. Cutaneous MAP observed in live pigs. The changes were graded as slight (1), moderate (2) or severe (3). Observations before day 26 showed no changes. Vertical lines show when therapy was introduced (cf. Table 1).

Group	Pig No.	Day									
		26	31	38	41	42	45	48	52	59	60
1	50	2									
	56		3[a,b]								
	58		1	1	2	2					
	63				1	2					
	65		1	1	1	2					
	70	1									
	72[c]										
	75	a	1[a]								
2	49	1	2[a]	1[a]	a						
	51	1	2	2			1				
	54		1	1							
	57		2								
	68	1	2	1							
	74		1								
3	52		1[a]								
	53		2								
	55	1	1								
	67	1	2	1							
	73	1	1								
	76										
4	59				1[a]	2[a]	1[a,b]				
	60						1[a]	1[a]	1[a]	1[a]	1[a]
	64			1	1[a]	2[a]	2[a]	2[a]	1[a]	1[a]	1[a]
	66							3	1	1	1

[a] Cutaneous edema.
[b] General icterus.
[c] Pig No. 72 died on day 25 without clinical signs of MAP.

As earlier reported (*Bengtsson et al.* 1976, *Hakkarainen et al.* 1978b), levels of blood selenium and serum glutathione peroxidase activity are found to be closely correlated in pigs. Serum GSH-Px activity exhibited also an excellent close-response relationship to dietary selenium. Therefore, it can be concluded that the estimation of glutathione peroxidase activity is reliable in evaluating the selenium status in pigs, and that the level of this enzyme reflects fairly well the changes of selenium in blood in the present investigation.

Table 3. Serum ASAT values (i.u./l). Underlined values indicate the serum ASAT values above normal upper limit (100 i.u./l). Vertical lines indicate when additives of selenium and tocopherol were included in the diet (cf. Table 1).

Group	Pig No.	Day													
		—1	10	13	17	26	31	38	41	42	45	48	52	59	60
1	50	47	26	22	23	306									
	56	33	26	33	50	1039	1158								
	58	56	29	21	25	50	58	113	263	307					
	63	50	25	39	33	30	33	79	685	777					
	65	46	51	70	31	30	42	58	1088	451					
	70	21	38	35	47	167									
	72	30	20	34	162										
	75	43	27	602	25	1153	725								
2	49	37	75	228	31	118	313	753	109		62	20	22	23	23
	51	47	58	25	24	106	162	109	67		149	47	27	26	28
	54	50	29	29	36	36	107	40	36		43	458	25	31	30
	57	36	28	24	37	56	154	79	36		33	26	23	25	26
	68	55	34	29	43	146	444	134	48		11	38	35	22	26
	74	38	37	25	40	38	109	94	64		270	125	22	46	39
3	52	33	25	25	73	66	96	53	31		27	78			
	53	42	55	25	47	72	323	73	45		71	26			
	55	38	33	24	29	45	163	59	28		52	55			
	67	39	26	29	28	192	1011	155	51		50	66			
	73	35	21	29	48	117	356	129	56		56	51			
	76	26	27	27	25	89	160	70	34		53	56			
4	59	34	37	25	31	35	28	71	783	1692	>1928				
	60	52	23	46	38	29	30	26	54	76	230	126	188	142	140
	64	76	22	31	28	36	40	113	1847	467	620	259	153	149	143
	66	42	29	50	35	29	62	54	403	1346	1911	913	235	162	208

Control pigs which were not given α-tocopherol or selenium supplement died within 44 days (Table 1). Mean survival time for this group was 34.4 ± 7.9 days (mean ± 1 s). In earlier experiments the survival time for corresponding control groups has also varied, probably depending on differences of starting levels of selenium and/or tocopheryl in pigs. The pigs of Sow 1077 weighed more than the pigs in the litters of the 2 other sows

Table 4. Glutathione peroxidase (GSH-Px) activity (μkat/l) in serum. Vertical lines show when therapy was introduced (cf. Table 1).

Group	Pig No.	Day										
		—1	13	26	31	38	40	41	45	48	59	60
1	50	4.3	4.1	2.1								
	56	4.4	3.5	2.6	1.9							
	58	7.3	4.9	4.1	3.9	3.0	2.6	2.0				
	63	6.8	3.7	3.3	2.7	3.0	2.5	1.8				
	65	6.8	4.5	4.3	4.1	3.3	2.1	2.8				
	70	5.4	4.6	2.5								
	72	3.4	2.8									
	75	4.7	4.1	2.8	2.1							
2	49	5.1	3.3	2.7	2.2	7.1	12.2		16.0	16.3	16.5	16.5
	51	5.1	4.1	3.0	2.6	8.5	13.5		18.1	18.7	19.4	19.5
	54	7.2	4.1	4.1	2.8	9.0	11.2		16.9	18.8	18.6	18.8
	57	5.3	3.6	3.6	1.7	9.1	12.3		14.2	17.0	18.0	18.4
	68	4.9	4.5	2.5	2.5	7.1	11.8		16.6	16.8	18.8	18.8
	74	4.4	4.3	2.9	2.4	5.9	11.0		13.1	14.6	16.2	16.6
3	52	5.6	5.6	3.5	2.0	6.5	12.8		17.0	19.7		
	53	6.4	5.1	4.1	1.8	8.9	12.7		19.2	20.0		
	55	6.0	5.1	3.2	2.0	6.1	13.4		18.0	19.0		
	67	4.0	2.7	2.4	2.6	5.1	7.6		11.0	12.5		
	73	5.2	4.2	4.1	2.4	5.3	14.4		16.3	16.0		
	76	5.5	5.5	4.0	2.2	5.4	12.0		12.9	14.9		
4	59	9.4	5.0	3.8	3.8	3.2	2.9	2.7	2.9			
	60	9.6	6.9	5.2	4.0	3.2	2.6	2.2	3.4	4.0	8.5	8.2
	64	9.4	5.5	3.1	3.7	2.7	3.0	2.4	1.8	3.2	7.2	6.5
	66	8.4	7.0	4.3	4.1	3.1	2.9	1.8	3.2	4.1	7.7	8.2

when the diet containing only traces of E-vitamin and selenium was introduced. It is obvious that the pigs of Sow 1077 (Nos. 58 to 66) had at the same time higher blood selenium concentrations than the pigs of Sow 1075 (Nos. 49 to 57) and Sow 1079 (Nos. 67 to 76) (Table 4). The difference in serum glutathione peroxidase activity on day —1 between the litter of Sow 1077 and the litters of Sows 1075 and 1079, respectively, was statistically significant ($P < 0.001$). The influence of the higher level of selenium status is reflected in the present investigation by the longer survival time of the pigs No. 58, No. 63 and No. 65 in Group 1, as well as in the longer time which elapsed before the pigs in Group 4 showed clinical signs of VESD and the therapy could be started (Tables 1, 2 and 3).

Table 5. Tocopherol in subcutaneous and abdominal fat on day of death (μg/g). Figures are mean of 2 individual determinations.

Group	Treatment	Pig No.	Died (d) or euthanized (e) on day	Subcutaneous fat	Abdominal fat
1	None	50	29 d		
		56	31 d	27.8	28.7
		58	44 d	14.8	13.8
		63	43 d	11.5	8.7
		65	44 d	16.8	14.0
		70	28 d		
		72	25 d		
		75	31 d	23.0	23.1
2	Days 0—31: None	49	60 e	16.1	15.9
	From day 32: 5 mg DL-α-tocopheryl	51	60 e	20.1	21.5
	acetate/kg and 135 μg Se (as	54	60 e	15.6	17.9
	sodium selenite)/kg food	57	60 e	18.3	20.2
		68	60 e	17.1	24.4
		74	60 e		
3	Days 0—31: None	52	48 e	21.6	32.1
	From day 32: 15 mg DL-α-tocopheryl	53	48 e	15.4	21.0
	acetate/kg and 135 μg Se (as	55	48 e	24.0	29.0
	sodium selenite)/kg food	67	48 e	25.2	28.4
		73	48 e	26.0	29.8
		76	48 e		
4	Days 0—41: None	59	47 d	20.7	18.7
	From day 42: 5 mg DL-α-tocopheryl	60	60 e	17.7	19.5
	acetate/kg and 45 μg Se (as	64	60 e		
	sodium selenite)/kg food	66	60 e		

Serum glutathione peroxidase (GSH-Px) activity decreased in Group 1, which received no supplement, as it did even in the other groups before the therapeutic treatment was introduced (Table 4). In Groups 2 and 3, which were given 135 μg selenium/kg diet from day 32, there was a pronounced and rapid increase in the GSH-Px activity following dietary supplementation of selenium, evidencing increased blood selenium in the treated pigs. The rate of recovery from the VESD syndrome was well related to this increase. In Group 4 the supplement of selenium, being but ⅓ of that in Groups 2 and 3, yielded an increase of blood selenium, but was not sufficient to promote recovery.

According to our unpublished observations, pig serum toco-

Table 6. Major necropsy findings. The changes are graded as slight (1), moderate (2) or severe (3).

Group	Pig No.	Hepatosis dietetica	Mulberry heart	Skeletal muscle degeneration	Cutaneous micro-angiopathy (MAP)	Gastric ulcer	Gastric para-keratosis
1	50	2	3	1	3		3
	56	2	3	3	3		
	58	1	3	1	3		
	63	1	3	3	3		
	65	1	2	3	2		
	70	3	2	1	1		2
	72	3	2				
	75	2	3	3	1		3
2	49						
	51						
	54						
	57		1				
	68		1				
	74						
3	52						
	53						
	55						
	67						
	73						
	76						
4	59	2	3	1	1		1
	60		2	1	1		
	64		2	2	1		
	66	1	2	2	1		

pherol as well as its total serum lipids are on a rather low level and serum tocopherol does not reflect the tocopherol status of the animal. This is in accordance with the conception of *Horwitt et al.* (1972) that serum tocopherol is closely correlated to the level of serum total lipid; as a consequence the conclusions on the nutritional tocopherol status of an animal based only on serum tocopherol are inadequate. Therefore, we have chosen the determination of tocopherol in subcutaneous and abdominal fat tissues as a more reliable measure of tocopherol status of the pig.

It is seen from Table 5 that the tocopherol content of fat decreased rapidly in control Group 1, which received no supplement of tocopherol. Thus, the values were about halved from day 31 to days 43 and 44. The supplement of 5 mg α-tocopheryl acetate/kg diet (Groups 2 and 4) was not sufficient to conserve the level in the fat observed on day 31 (Group 1), but it prevented the rapid decrease which was seen in unsupplemented pigs. The supplementation of 15 mg α-tocopheryl acetate/kg diet (Group 3) was apparently just sufficient to maintain the tocopherol stores at an unchanged level. However, it should be pointed out that some decrease of stores could already have taken place during the first 31 days without tocopherol supplementation.

The distribution of pathological changes is illustrated in Table 6. The control pigs (Group 1) exhibited the typical VESD post-mortem pattern. Hepatosis dietetica, mulberry heart, skeletal muscle degeneration, cutaneous microangiopathy and gastric parakeratosis were common findings. Gastric ulcers, however, were lacking.

The euthanized pigs in Groups 2 and 3, which received therapy, showed only sporadic pathological changes. Slight myocardial damage of chronic character was observed in 2 pigs. It is probable that the pigs received these myocardial changes before the supplementation of α-tocopherol and selenium started.

Even the necropsy findings indicated that the therapy of the pigs in Group 4 was insufficient and did not heal the VESD injuries, i.e. mulberry heart, skeletal muscle degeneration, cutaneous microangiopathy, hepatosis dietetica and gastric parakeratosis during the time of observation.

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SAMMANFATTNING

Kombinerad terapeutisk effekt av dietärt selen och vitamin E på manifesterat vitamin E- och selenbrist (VESD)-syndrom hos avvanda grisar.

Fodret åt avvanda grisar, vilka hade insjuknat i experimentellt framkallat vitamin E- och selenbrist (VESD)-syndrom, supplementerades i terapeutiskt syfte med α-tokoferylacetat och selen. Samma mängder av vitamin E och selen visade sig vara verksamma vid användning i terapi som i profylax. Resultaten gav således stöd åt slutsatsen att 5 mg DL-α-tokoferylacetat och 135 µg selen/kg foder, vilket ursprungligen innehåller endast spår av vitamin E och selen representerar ett minimibehov av dessa ämnen för avvanda grisar. Glutationperoxidas-aktiviteten i blodserum användes som ett mått på grisarnas selenstatus. En modifierad metod för bestämning av tokoferol i fettvävnaden beskrevs. Tillsättning av 15 mg α-tokoferylacetat/kg foder visades vara tillräckligt för att behålla kroppsfettets tokoferolförråd på oförändrad nivå.

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